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Synthesis and application of chiral hydrobenzoin

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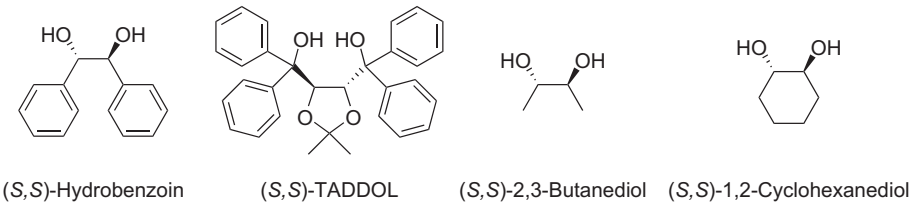
1. Introduction

Chiral control in organic chemistry is a central theme in both academia and industry. In asymmetric synthesis, C_2-symmetrical molecules have been employed as a chiral origin for a long time. As chiral ligands or auxiliaries, many kinds of C_2-symmetrical molecules, such as bisphosphine, diamine, biphenol, and diene have been applied to various chiral syntheses. Chiral diols share also an important position in asymmetric synthesis, as chiral ligands, auxiliaries, and chiral synthetic blocks. The industrially available chiral diols are summarized in Scheme 1. Among them, hydrobenzoin (1,2-diphenyl-1,2-ethanediol) and its derivatives have been used in various areas of chiral chemistry and have broadened their range of applications in synthetic chemistry. Fig. 1 shows the number of articles on these chiral diols between 1997 and 2009 in Chemical Abstract. The increase in the number of articles that are related to chiral hydrobenzoin shows its usefulness and versatility in chiral technology.



Scheme 1. Industrially available chiral diols.

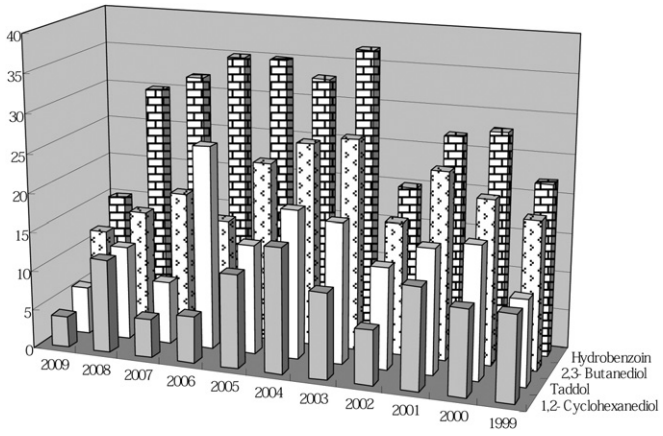


Fig. 1. The number of articles on chiral diols.

This review summarizes the synthesis and the application of hydrobenzoin. The review by Sharpless on the catalytic dihydroxylation contains examples of the preparation and application of hydrobenzoin before 1994.[1] Joshi also reported a review of the chemistry of C_2-symmetrical chiral diols in 2006.[2] This review focuses on the chemistry of hydrobenzoin and its derivatives and covers the historical background to its updated utilization.

In process chemistry, the industrial availability and cost of the starting material are very important for the design of the synthetic route, and especially the cost of the chiral source is often the critical factor of the choice of asymmetric synthesis. Table 1 summarizes the reagent price of representative C_2-symmetrical chiral diols in the Aldrich catalog. Chiral hydrobenzoin is one of the cheapest chiral diols, which are procurable in kilogram quantities. Recent advances of preparation methods have also enhanced the application of hydrobenzoin and its derivatives.

Table 1
The reagent prices of chiral diols (Sigma–Aldrich)

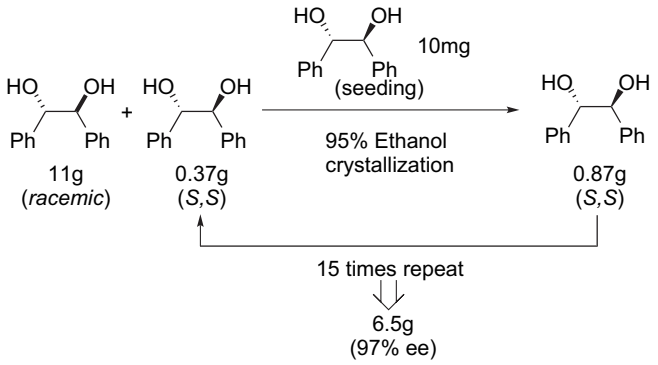
Compounds	Fw	Weight (g)	Price		
			USD/btl.	USD/g	USD/mol
(*R*,*R*)-Hydrobenzoin	214.26	25	227.5	9	1950
(*S*,*S*)-Hydrobenzoin	214.26	25	312.5	13	2678
(2*R*,3*R*)-2,3-Butanediol	90.12	25	191	38	3443
(2*S*,3*S*)-2,3-Butanediol	90.12	25	449.5	90	8102
(1R,2R)-trans-1,2-Cyclohexanediol	116.16	1	228	228	26484
(1S,2S)-trans-1,2-Cyclohexanediol	116.16	1	244	244	28343
(R,R)-TADDOL	466.57	1	114	114	53189
(S,S)-TADDOL	466.57	1	161.5	142	66253

2. Synthesis of chiral hydrobenzoin and its derivatives

2.1. Resolution of racemic hydrobenzoin

2.1.1. Optical resolution by direct crystallization. Hydrobenzoin has a long history from the beginning of chiral chemistry; it was one of the few compounds that could be resolved by direct crystallization—the phenomena that Pasteur had found in sodium ammonium tartarate tetrahydrate.[3] The resolution of *dl*-hydrobenzoin by direct crystallization was observed for the first time by Erlenmeyer, in 1897.[4] Fieser described the resolution of hydrobenzoin by hand sorting in his famous textbook, 'Experiments in Organic Chemistry'.[5] This textbook shows the photograph of both crystals of (*R*,*R*)-hydrobenzoin and (*S*,*S*)-hydrobenzoin obtained by direct crystallization. Ramsey also reported the resolution by direct crystallization of *dl*-hydroveratroin (1,2-bis(3,4-dimethoxyphenyl)-1,2-ethanediol). *dl*-Hydroveratroin was allowed to crystallize slowly from aqueous ethanol, and several well-formed crystals were selected and allowed to grow slowly in contact with the mother-liquors. Each single crystal of 5–10 mg corresponded to either enantiomer.[6]

Based on these characteristics, Brienne reported the preferential crystallization of chiral hydrobenzoin from a racemic mixture by the seeding of the chiral crystal (Ref. 3, Scheme 2). Racemic hydrobenzoin (11 g) is dissolved along with 0.37 g of (*S*,*S*)-



Scheme 2. Direct resolution by seeding.[3]

hydrobenzoin in 85 g of 95% ethanol, and the solution is cooled to 15 °C. Seeds of (*S*,*S*)-hydrobenzoin (10 mg) are added and stirred the solution to crystallize for 20 min. The weight of (*S*,*S*)-hydrobenzoin (0.87 g), which is obtained after filtration was roughly doubled from the amount of the (*S*,*S*) form added in excess at the beginning of the experiment. The same cycle of operations, i.e., loading with racemic hydrobenzoin and collection of (*R*,*R*) and (*S*,*S*) crystals, is carried out 15 times, yield 6.5 g of (*S*,*S*) and 5.7 g of the (*R*,*R*) enantiomer, each having about 97% optical purity. Based on this principle, Brugidou described the apparatus for the continuous resolution of racemic hydrobenzoin (Fig. 2).[7] This device is made up of two jacketed tubes, A and B, which are maintained at different temperatures with the circulation of hydrobenzoin solution. A seed of one enantiomer is introduced in tube B. The crystal of the corresponding enantiomer grows and is separated in tube C.

Recently, Maillard disclosed a new method, 'Particle-size-controlled crystallization'.[8] In the preferential crystallization of chiral hydrobenzoin, they used a mixture of enantiomers as seed crystals, where an enantiomer differed in size or in quantity from the other enantiomer, to allow the separation of the crystals composed of a mixture enriched with a enantiomer and isolated by size separation such as sieving.

2.1.2. Optical resolution by diastereomer formation. The resolution of racemic compounds using the formation of crystalline diastereomer is the standard method in the preparation of chiral compounds; however, literature using this methodology in the preparation of chiral hydrobenzoin is limited (Scheme 3). Knollmüller reported the resolution of hydrobenzoin via acetal

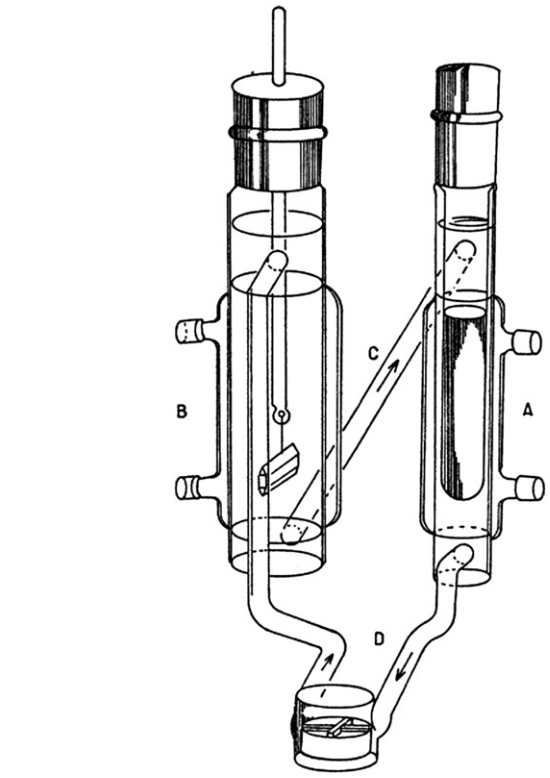
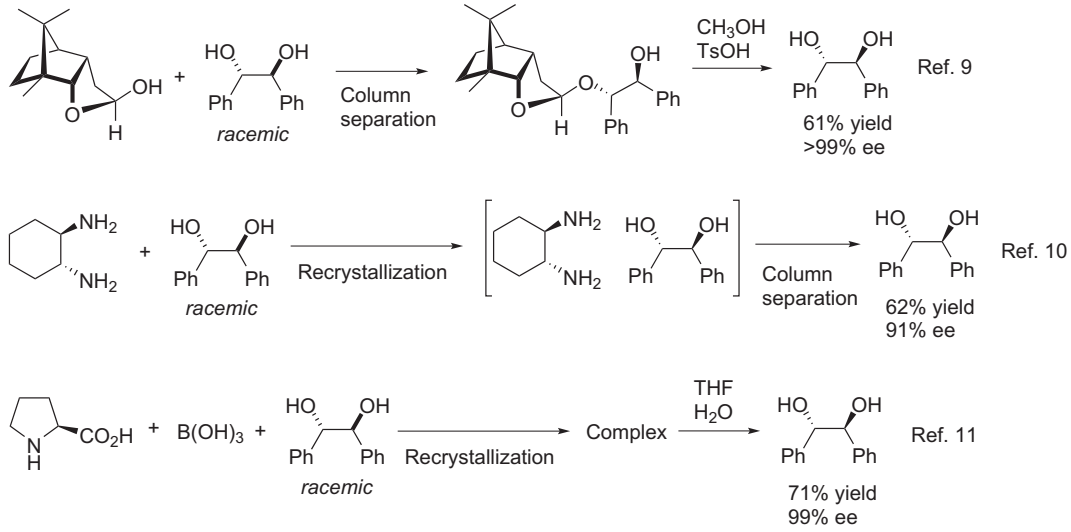


Fig. 2. Apparatus of the continuous resolution of hydrobenzoin.[7]

formation with chiral (3a,*S*)-2α-hydroxy-7,8,8-trimethyloctahydro-4,7-methanobenzofuran.[9] In 1991, Kawashima reported that racemic hydrobenzoin makes a diastereomeric complex with chiral 1,2-cyclohexanediamine by hydrogen bonding and that both diastereomers can be separated by crystallization.[10] The decomposition of the separated diastereomer complex occurs by acid treatment only; therefore, enantiomerically pure hydrobenzoin can be obtained by simple work-up. Similarly, Periasamy reported the resolution through complexation with (*S*)-proline and boronic acid; however, the structure of complex was not reported.[11]

2.1.3. Kinetic resolution of racemic hydrobenzoin. During this decade, the kinetic resolution of racemic 1,2-diols by selective acylation of hydroxyl groups has advanced. In 2003, Matsumura reported the



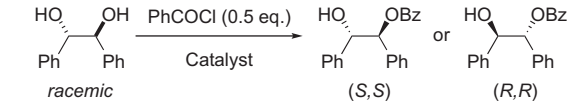
Scheme 3. Optical resolution via diastereomer formation.

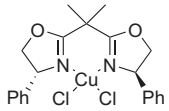
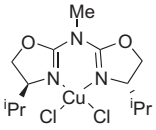
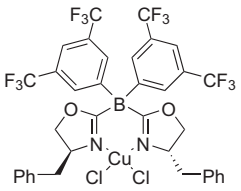
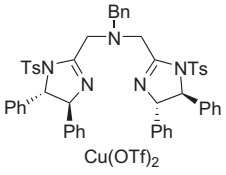
kinetic resolution of 1,2-diols by asymmetric benzoylation, catalyzed by a chiral copper complex.[12] They considered that a chiral organometallic catalyst discriminates the hydroxyl group of 1,2-diol, and generates a diastereomeric metal alkoxide to be acylated and they found that Ph-box–$CuCl_2$ catalyzed the asymmetric monobenzoylation of racemic hydrobenzoin. If aryl group is included in both diol and acyl chloride, an *s*-value reaches up to 645. The benzoylation of *dl*-hydrobenzoin in the presence of an excess amount of (*R*,*R*)-catalyst gave an (*S*,*S*)-benzoyl ester with 98% ee. This result suggests that enantio-discrimination mainly took place at the acylation step, not on contact of the catalyst. Following the report by Matsumura, the kinetic resolution of 1,2-diol by the same concept was reported by Majoral (azabis(oxazoline)),[13] Pfaltz (boron-bridged bisoxazoline (Borabox))[14], and Arai (*N*-tethered bis(imidazoline))[15] (Scheme 4). On the other hand, Fujimoto reported that the phosphinite derivative of quinidine catalyzed the kinetic resolution of racemic hydrobenzoin by benzoylation (Scheme 5).[16] In this case, it was postulated as a possible reaction mechanism that the phosphinite moiety activates acyl chloride as a Lewis base, and that the nitrogen atom of quinuclidine acts as a Brønsted base to form alkoxide by enantio-discriminative process.

Besides acylation, Onomura tried selective oxidation of the hydroxyl group of racemic hydrobenzoin in the presence of the same type of bisoxazoline catalyst, but the selectivity was modest (Scheme 6).[141]

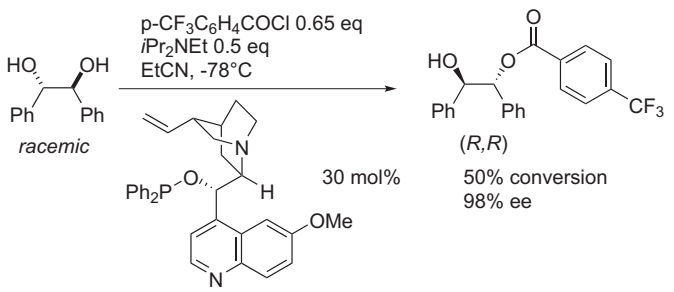
2.2. Asymmetric dihydroxylation of *trans*-stilbene

In the 1980s, Sharpless developed the asymmetric dihydroxylation of olefins using osmium tetroxide with a chiral cinchonidine catalyst, and this reaction became the standard procedure for the synthesis of chiral 1,2-diols from olefins. *trans*-Stilbene is a good substrate for this reaction; therefore, Sharpless reported kilogram-scale preparations of enantiopure hydrobenzoin from *trans*-stilbene (Scheme 7).[142] By this reaction, the availability of chiral hydrobenzoin is dramatically improved and has become the trigger to explore the

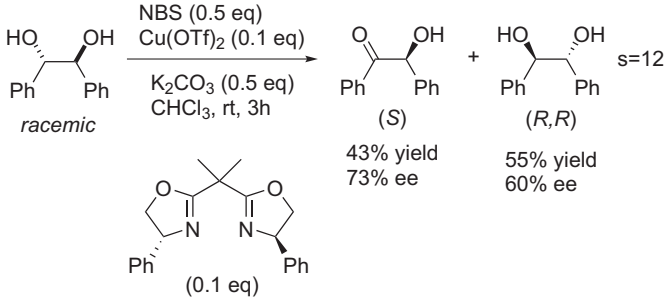


Catalyst	Product	Result	Ref.
	(*S*,*S*)	48% yield 99% ee s=>645	12
	(*R*,*R*)	45% yield 99% ee	13
	(*R*,*R*)	51% yield 96% ee S=225	14
	(*S*,*S*)	28% yiled 48% ee	15

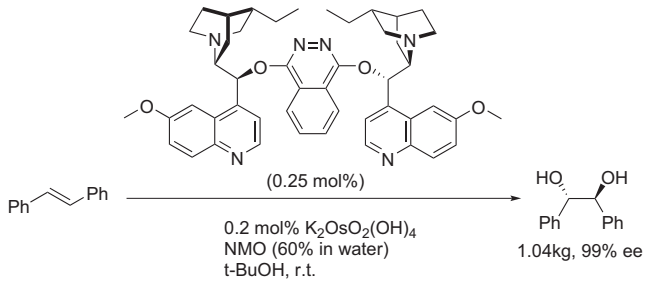
Scheme 4. Kinetic resolution by asymmetric benzoylation.



Scheme 5. Kinetic resolution catalyzed by amine-phosphinite bifunctional organocatalysis.[16]



Scheme 6. Kinetic resolution by asymmetric oxidation.[141]



Scheme 7. Sharpless asymmetric dihydroxylation of stilbene.[142]

application of chiral hydrobenzoin in many groups. Sharpless also summarized the application of chiral 1,2-diol, including hydrobenzoin in organic synthesis; therefore, the application of hydrobenzoin in the area of asymmetric synthesis has increased considerably after this review (Ref. 1). Moreover, because stilbene became the standard substrate in the research of asymmetric dihydroxylation, many literatures that describes the preparation of chiral hydrobenzoin by this reaction has been reported to date.

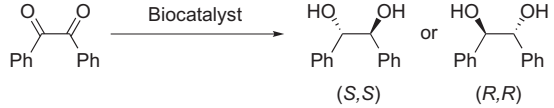
The problems in asymmetric dihydroxylation are the cost of the chiral ligands and the consequent contamination by osmium. To address these problems, several groups reported immobilization or heterogenization of this catalytic system,[143] including polymeric cinchona alkaloids,[17] osmium complexes supported on MCM-41 zeolites,[18] and PEGylated ionic polymer-supported osmium tetroxide.[19]

2.3. Asymmetric reduction of benzil or benzoin

Asymmetric reduction of carbonyl compounds is currently the most popular method for the preparation of chiral alcohols. Many kinds of catalytic methods, including chemocatalyst and biocatalyst, have been used as the practical process. In this chapter, the history and the current progress of asymmetric reduction of benzil or benzoin are summarized.

2.3.1. Biocatalytic asymmetric reduction of benzil or benzoin. The first report of 'asymmetric' synthesis of hydrobenzoin was the biocatalytic reduction of benzil by Prelog in 1965 (Table 2).[20] He investigated the asymmetric reduction of benzil by *Curvularia falcate* and reported that (*S*,*S*)-hydrobenzoin was obtained in high optical yields, but approximately equal amounts of *meso*-hydrobenzoin was also formed. Prelog's work was not noticed as the preparation method, but the result of the selectivity contributed to the establishment of 'Prelog's rule,' a general rule for the selectivity of the reaction of the carbonyl carbon adjacent to the chiral center.

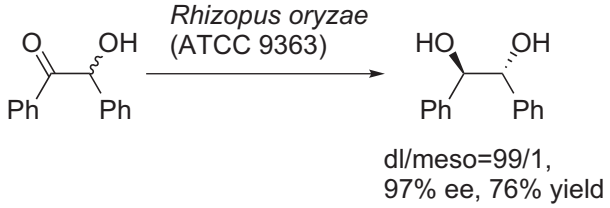
Table 2
Biocatalytic asymmetric reduction of benzil



Biocatalyst	Reaction time (days)	dl/*meso*	Ee (%)	Yield (%)	Ref.
Curvularia falcate		50/50	NR (*S*,*S*)		20
C. macerans	7	95/5	99 (*R*,*R*)		21
R. mucilaginosa	3–5	82/18	98 (*R*,*R*)	81	22
R. oryzae (ATCC 9363)	21	99/1	99 (*R*,*R*)	77	23

Thirteen years later, Ziffer reported that *Cryptococcus macerans* reacted with benzils and yielded (*R*,*R*)-hydrobenzoins of high optical purity and diastereoselectivity.[21] When racemic benzoin was used as the substrate, (*R*,*R*)-hydrobenzoin greater than 50% was obtained and (*S*)-benzoin was recovered. These results can be explained by dynamic kinetic resolution, namely, the biocatalyst reduces (*R*)-benzoin more rapidly under the conditions of the racemization of benzoin. In 1986, Buisson also reported various yeast strains and found that *Rhodotorula mucilaginosa* afforded high yields of (*R*,*R*)-hydrobenzoin.[22] He also observed the dynamic kinetic resolution; however, the yield from racemic benzoin was modest due to the by-production of the *meso*-form.

In 2004, Demir reported that the fungus *Rhizopus oryzae* (ATCC 9363) gave (*R*,*R*)-hydrobenzoin from benzil with high selectivity (dl/*meso*=99/1, 99% ee, 77% yield).[23] Racemic benzoin was also used as a substrate and was converted to (*R*,*R*)-hydrobenzoin (dl/*meso*=99/1, 97% ee, 76% yield) with dynamic kinetic resolution (Scheme 8). There is a big room for improvement in the long reaction time (benzil: 21 days) and low reaction concentration (0.5 mmol/100 ml); however, Demir's work shows the potential of the biocatalytic reduction of benzil or benzoin as the preparation method for chiral hydrobenzoin.

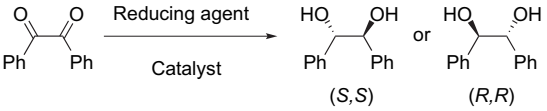


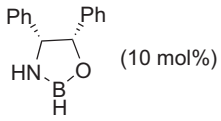
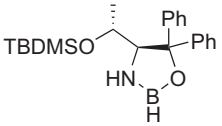
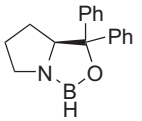
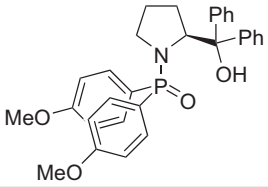
Scheme 8. Enzyme catalyzed dynamic kinetic resolution of benzoin.[23]

2.3.2. Chemocatalytic asymmetric reduction of benzil or benzoin. Now, the asymmetric reduction of carbonyl compound is the most promising and feasible method for the preparation of chiral alcohols. The chemocatalytic method is the most widely used in this area; however, it was necessary for the chemocatalytic asymmetric reduction of benzil to improve the diastereoselectivity, namely, the suppression of *meso*-diol formation. In 1983, Yamagishi first reported the formation of chiral hydrobenzoin by the asymmetric reduction of benzil using colloidal particles of Δ-Ni $(phen)_3^{2+}$–montmorillonite (phen=1,l0-phenanthroline) acting as asymmetric templates; however, the enantioselectivity was not reported.[24] Chiral Ru–Binap complexes, representative chiral catalysts in the carbonyl reduction developed by Noyori, gave *meso*-hydrobenzoin as the major product. This reason was that the substrate control favored *meso*-diol formation in the second hydrogenation step of the hydroxyketone intermediate.[25]

Several groups reported that the oxazaborolidine-catalyzed reduction of benzils yielded chiral hydrobenzoin; however, suppression of *meso*-diol was a challenging theme (Table 3). Quallich reported the first systematic examination of the asymmetric reduction of various 1,2-diketone by diphenyl oxazaborolidine; however, benzil showed moderate diastereoselectivity and enantioselectivity.[26] Although Fujisawa's L-threonin-derived oxazaborolidine showed good enantioselectivity, diastereoselectivity was not improved.[27] Joshi found that the formation of *meso*-form was due to the intramolecular hydride transfer from the initially formed OBH_2 group and estimated that faster rate of the catalyzed reduction gave better diastereoselectivity. As a consequence, Joshi found that a borane–methyl sulfide complex provided higher diastereoselectivity.[28] On the other hand, Wills reported phosphinamide catalysts that, in contrast to oxazaborolidines, exerted a catalytic effect primarily through Lewis base interactions of the phosphinamide oxygen atom with the borane-reducing agent. This catalyst also shows good selectivity in the asymmetric reduction of benzil.[29]

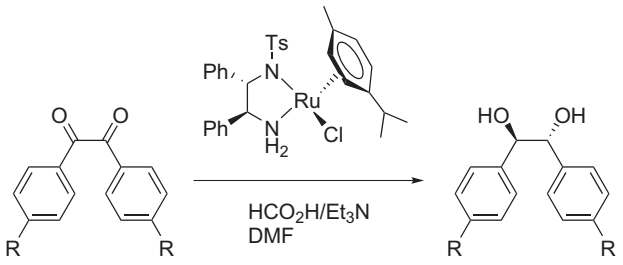
Table 3
Chemocatalytic reduction of benzil by oxazaborolidines



Reducing agent	Catalyst	dl/*meso*	ee (%)	Yield (%)	Ref.
BH_3/THF	 (10 mol%)	52/48	85 (*R*,*R*)		26
BH_3/THF	 (20 mol%)	50/50	>99 (*S*,*S*)	99	27
BH_3/Me_2S	 (10 mol%)	88/12	>99 (*S*,*S*)	85	28
BH_3/Me_2S	 (10 mol%)	86/14	>90 (*S*,*S*)	83	29

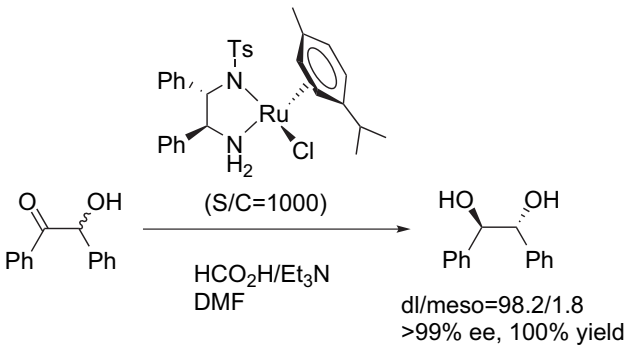
In 1999, we found that asymmetric transfer hydrogenation of benzil using a ruthenium catalyst gave chiral hydrobenzoin at high selectivity (Table 4).[30] The asymmetric transfer hydrogenation of benzils, catalyzed by RuCl(Tsdpen)(η^6-*p*-cymene) (Tsdpen: *N*-(*p*-toluenesulphonyl)-1,2-diphenylethylenediamine) with a formic acid/triethylamine mixture, gave hydrobenzoin with excellent diastereomeric and enantiomeric purity. The use of RuCl(Tsdpen)(η^6-mesitylene) and RuCl(Tscydn)(η^6-*p*-cymene) (Tscydn: *N*-(*p*-toluenesulphonyl)-1,2-cyclohexanediamine) has the same effect on this reaction. Formic acid is the best hydrogen donor for this reduction process. Enantiomerically pure hydrobenzoin was obtained with a high isolated yield by the simple evaporation of triethylamine, followed by washing with water and crystallization from methanol. Various benzil derivatives, bearing substituents on aromatic rings, can be stereoselectively reduced to chiral hydrobenzoin with a high enantiomeric excess and a good yield. Benzils with electron-donating substituents were reduced with excellent enantioselectivity but with lower reactivity, while the reduction of *p*-fluorobenzyl proceeded rapidly as expected, yielding a product with high enantiomeric excess.

Table 4
Asymmetric transfer reduction of benzils[30]



R	S/C	Temp (°C)	Time (h)	dl/*meso*	ee (%)	Yield (%)
H	1000	40	24	98.4/1.6	>99	100
CH_3	1000	40	48	96.7/3.3	>99	67
OCH_3	200	35	48	94.4/5.6	>99	75
F	1000	40	24	94.2/5.8	>99	100

The success of the asymmetric reduction of benzils with a mixture of formic acid and triethylamine relies strongly on the configurationally labile stereogenic center of benzoin, the chiral structure, and the functional group discriminating ability of the chiral ruthenium complexes. Thanks to the rapid interconversion of the stereochemistry of benzoin under the reaction conditions, the dynamic kinetic resolution of benzoin allows for the diastereo- and enantioselective synthesis of chiral hydrobenzoin and the dynamic kinetic resolution of benzoin.[31] Thus, the reaction of racemic benzoin in a mixture of formic acid and triethylamine containing (*S*,*S*)-catalyst yields (*R*,*R*)-hydrobenzoin quantitatively (Scheme 9). The asymmetric reduction of benzils or benzoins is the most practical method in the preparation of chiral hydrobenzoin. In particular, this method is highly effective for preparing substituted hydrobenzoin, because various substituted benzils and benzoins are commercially available. Now, chiral hydrobenzoin is produced commercially by this method at Kanto Chemical in Japan.[32]

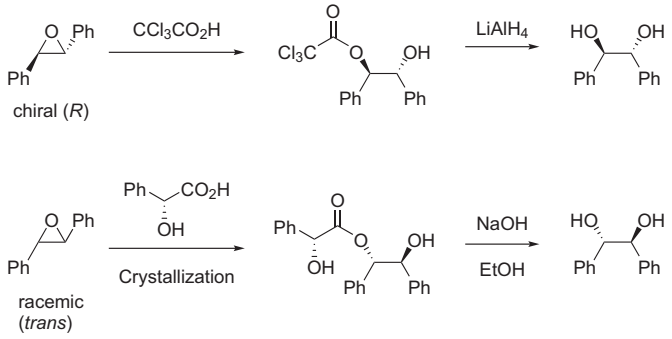


Scheme 9. Ruthenium catalyzed dynamic kinetic resolution of benzoin.[31]

A recent advance in asymmetric transfer hydrogenation is the use of water as the solvent. Xiao reported that an MTsdpen (M=Rh, Ir)/HCO_2Na system shows excellent reactivity and selectivity for a wide range of ketones, including benzil.[33]

2.4. Ring opening of stilbene oxide

Ring opening of stilbene oxide is a classical method for the preparation of hydrobenzoin. Ring opening of *trans*-stilbene oxide by oxygen nucleophile proceeds *syn*-selectively; therefore, it affords racemic hydrobenzoin whenever oxygen attacks either benzyl carbon. If chiral stilbene oxide is used as the substrate, the ring opening reaction naturally affords single enantiomers of hydrobenzoin, as reported by Berti already in 1960.[34] This methodology was inconspicuous behind Sharpless asymmetric dihydroxylation; however, it would be useful today, because chiral stilbene oxide is now easily prepared by several methods. When the chiral oxygen nucleophile reacts with a racemic mixture of *trans*-stilbene oxide, the diastereomer mixture can be separated to form chiral hydrobenzoin. Collet reported that the ring opening of *trans*-stilbene oxides by (+)-mandelic or (+)-camphanic acids followed fractional crystallization and that saponification gave (*R*,*R*)-hydrobenzoin (Scheme 10).[35]

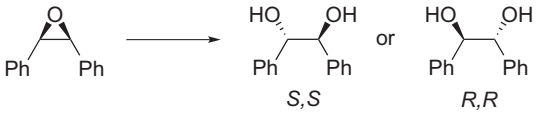


Scheme 10. Ring opening of *trans*-stilbene by oxygen nucleophile.[34,35]

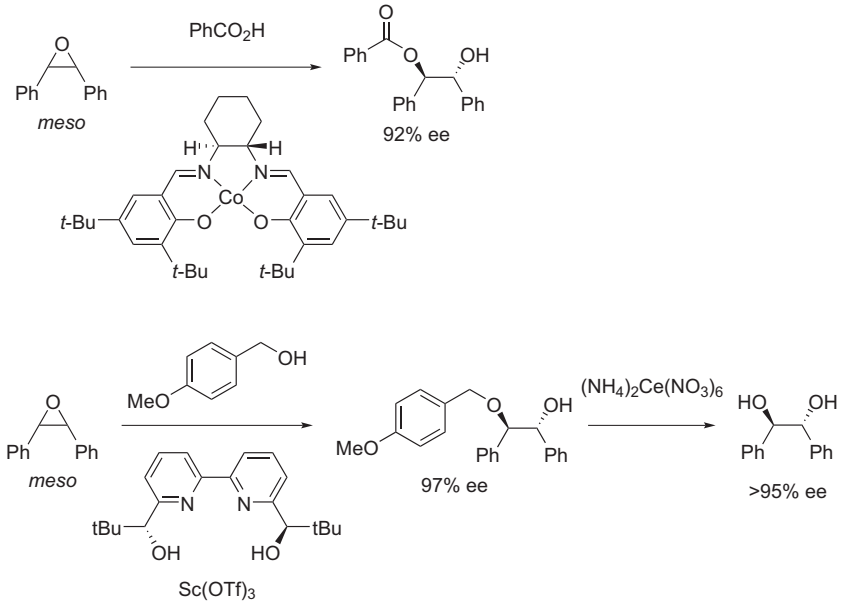
In the case of *meso* stilbene oxide, the selection of benzyl carbon by an oxygen nucleophile, i.e., 'desymmetrization' technology, is needed to produce chiral hydrobenzoin. The desymmetrization of *meso* stilbene oxide is achieved by both chemocatalysis and enzyme. The chiral Co(salen) complex of Jacobsen is effective for asymmetric ring opening of *meso* stilbene oxide with benzoic acid.[36] Recently, Schneider reported that a complex comprising scandium–bipyridine can catalyze the alcoholysis of *meso* epoxide with good yield and enantioselectivity.[37] The resulting monoalkoxy hydrobenzoin can be transformed into hydrobenzoin by deprotection (Scheme 11).

The enzymatic desymmetrization of *meso* stilbene oxide has had a longer history than chemocatalysts. In the 1970s, 'epoxide hydrase' had the attention in the metabolism pathway of organic compounds, and *meso* stilbene oxide was used as the model compound in the research of the mechanism of biological hydration. Watabe reported that *meso* stilbene oxide was hydrolyzed to (*R*,*R*)-hydrobenzoin by microsome epoxide hydrase.[38] Dansette also examined the effect of an aryl substituent on the rate at which epoxide hydrase catalyzed the addition of water to *meso* stilbene oxides, and found that a nucleophilic attack occurred and that a free carbonium ion form of the substrate was not involved in the rate-determining step in the mechanism.[39] Belucci also reported the enzymatic hydrolysis of *meso* stilbene oxide with rabbit liver microsomes; however, the optical purity of the produced *R*,*R*-hydrobenzoin was 87%.[40] However, these works were a matter for biochemical research, and were not examined on a preparative scale. After a blank period for 10 years, Burk reported an improved enzymatic system to form both (*R*,*R*) and (*S*,*S*)-hydrobenzoin from *meso* stilbene oxide on a preparative scale.[41] He demonstrated that (*R*,*R*)-hydrobenzoin was prepared on a gram scale by the enzyme BD8877. The results of enzymatic hydration of *meso* stilbene oxide are summarized in Table 5.

Table 5
Enzymatic desymmetrization of *meso* epoxide



Biocatalyst	ee (%)	Configuration	Ref.
MEH	99	*R*,*R*	38
MEH	99	*R*,*R*	39
MEH	87	*R*,*R*	40
BD8877	99	*R*,*R*	41
BD9126	99	*S*,*S*	41

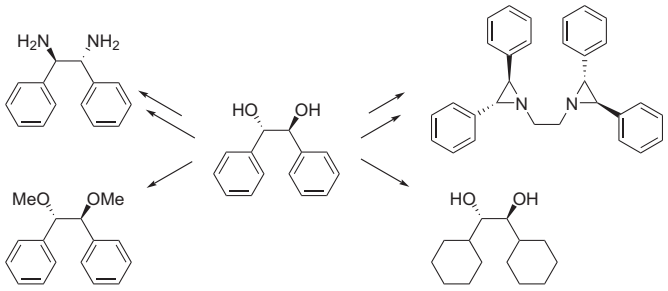


Scheme 11. Desymmetrization of *meso* stilbene by chemocatalysis.[36,37]

2.5. Asymmetric pinacol coupling of benzaldehyde

The asymmetric pinacol coupling of benzaldehyde would be the most efficient and economical route because of the good availability of the benzaldehyde and a short reaction step. After the first report of pinacol coupling reactions that were mediated with a stoichiometric amount of titanium reagent in 1973 by Mukaiyama, a number of reaction systems employing stoichiometric amounts of chiral reagents were reported. Matsubara reported enantioselective pinacol coupling with titanium(II) chloride with enantiopure tertiary amines or vicinal diamines as additives; however, the enantiomeric excess of hydrobenzoin was 0–41%.[42] By using proline-based chiral amines, Enders first reported that the asymmetric pinacol coupling of aromatic aldehydes stably proceeded and afforded 1,2-diols in moderate selectivity.[43] Although a stoichiometric reagent was also needed, Riant found that a titanium phenolate–chiral Schiff base complex showed high diastereoselectivity; this work became a base of the subsequent catalyst design.[44]

During this decade, catalytic asymmetric pinacol coupling has been advanced (Table 6). In 2003, Joshi first reported catalytic asymmetric pinacol coupling using a Ti–SALEN complex.[45] The Ti(IV)–SALEN complex can be easily prepared by mixing titanium tetraisopropoxide with SALEN, followed by ligand exchange with trimethylsilyl chloride. Reduction of the Ti(IV) complex with Zn generates a Ti(III) species that reacts with aldehyde to produce chiral titanium alkoxide of hydrobenzoin. Treatment by trimethylsilyl chloride produces disilyl hydrobenzoin, regenerates the Ti(IV) complex, and, following desilylation by TBAF, affords chiral hydrobenzoin. Zhu reported that the complex derived from Mo[46] and V[47] also works as an effective precatalyst for asymmetric pinacol coupling. A SALEN-type ligand bearing pyridine was also reported by You.[48] Yamamoto created a very unique ligand bearing bis-quinolinol, linked by a binaphthyl backbone, and showed good enantioselectivity at low catalyst loading when chromium was used as the catalyst metal.[49] These works revealed that asymmetric pinacol coupling is potentially a practical route for preparing chiral hydrobenzoin.

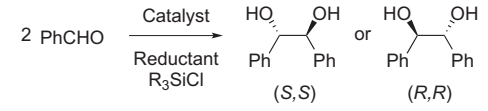


Scheme 12. Derivatization of chiral hydrobenzoin.

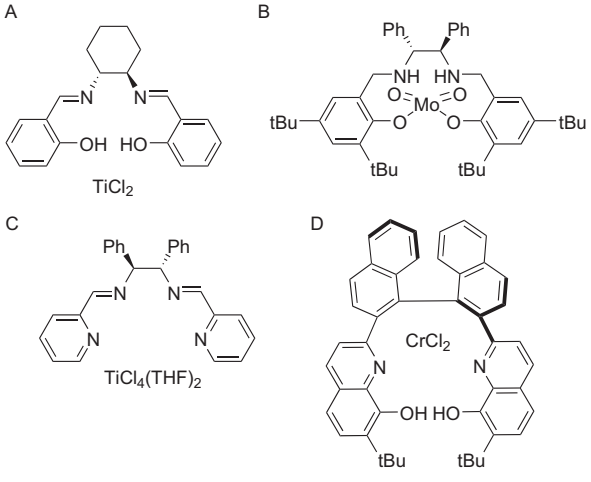
azidation and reduction, is used as the chiral ligand for various asymmetric reductions, including asymmetric hydrogenation, asymmetric transfer hydrogenation, and asymmetric oxidation. As mentioned in the preceding chapter, asymmetric transfer hydrogenation is useful for the preparation of chiral hydrobenzoin. Therefore, asymmetric transfer hydrogenation, using it as the catalyst reproduce chiral hydrobenzoin. The chemistry of 1,2-diphenyl-1,2-ethylenediamine is summarized by Noyori.[50] As the same nitrogen ligand, Andersson prepared C_2-symmetric bisaziridines from hydrobenzoin in two steps and showed their utility as chiral ligands in a variety of asymmetric transformations using transition metals, including osmium (dihydroxylation), palladium (allylic alkylation), and copper (cyclopropanation and aziridination).[51] The bisether ligand (Tomioka ether) is often used in the reaction of organolithium, described in the section on asymmetric conjugate addition (Section 3.2.3). Hydrogenation of benzene nuclei of hydrobenzoin gives 1,2-dicyclohexyl-1,2-ethanediol. This ligand is used mainly in asymmetric insertion reactions (Section 3.1.1.9).

The orthosubstituted analog of hydrobenzoin often indicates improved stereoselectivity compared with non-substituted ones. As is explained in the chemistry of asymmetric sulfide oxidation in Section 3.2.6, *o*-bromohydrobenzoin shows higher enantiomeric excess than the simple hydrobenzoin ligand. Recently, Britton

Table 6
Catalytic asymmetric pinacol coupling of benzaldehyde

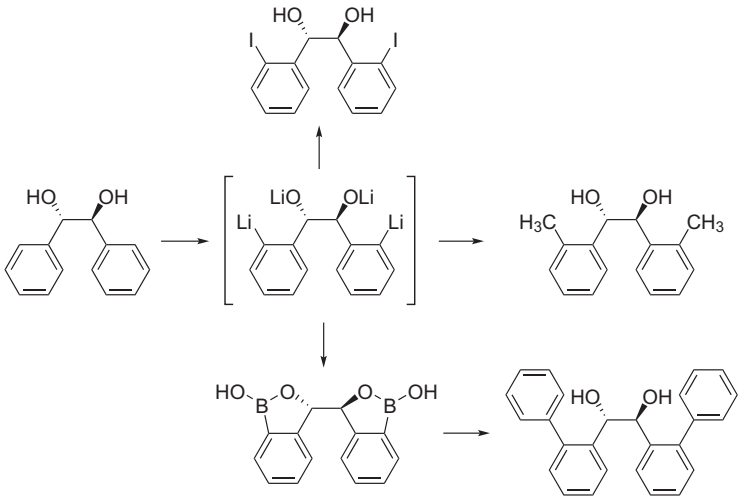


Cat. (mol%)	Reductant	R_3SiCl	Yield (%)	dl/meso	ee (%)	Ref.
A (10)	Zn	TMSCl	94	98/2	95 (*R,R*)	45
B (15)	Zn	TMSCl	90	92/8	95 (*S,S*)	46
C (15)	Mn	TMSCl	96	95/5	90 (*S,S*)	48
D (3)	Mn	TESCl	94	98/2	97 (*R,R*)	49



2.6. Derivatization of hydrobenzoin

Hydrobenzoin is often used as its derivatives for various applications (Scheme 12). The examples until 1994 are summarized by the review by Sharpless.[1] 1,2-Diphenyl-1,2-ethylenediamine, which is prepared by the mesylation of hydrobenzoin, followed by reported bidirectional *ortho* metalation of hydrobenzoin by alkyl lithium (Scheme 13).[52] He found that non-protected hydrobenzoin gave a tetraanion by treatment with an excess amount of butyl lithium. This tetraanion is trapped by various electrophiles to give *ortho*-functionalized hydrobenzoin derivatives. Interestingly, bis-benzoxaborol, obtained from the reaction with trimethyl



Scheme 13. The preparation of *ortho*-substituted hydrobenzoin.[52]

borate, provides an access to a new biaryl type of chiral hydrobenzoin. This new type of ligand is expected to broaden the utility of hydrobenzoin.

3. Application in asymmetric synthesis

The versatility of hydrobenzoin in chiral chemistry can be attributed to the nature of the oxygen atom and two aryl groups. The coordination ability of oxygen to metal ions, or the synthetic usefulness as a nucleophile or leaving group, shows unique features in asymmetric synthesis, which is different from other chiral ligands. In this section, the application of hydrobenzoin in asymmetric synthesis is summarized.

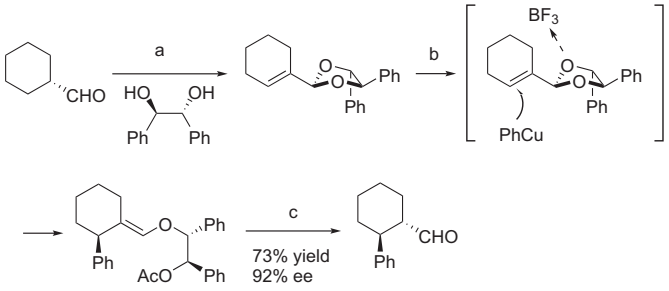
3.1. Stoichiometric application in asymmetric synthesis

Owing to a rigid chiral structure of the diphenylethylene group, multifunctional diol groups, and its good availability, hydrobenzoin has been employed as a stoichiometric agent in asymmetric synthesis for a long time. Hydrobenzoin can be easily installed as a ketal, acetal, ether or ester to the substrate by the linkage of the hydroxyl group. After the substrate is transformed enantioselectively by the stereochemical effect of the chiral structure of hydrobenzoin in the neighboring group, hydrobenzoin is removed. Usually, it is easily removed by hydrolysis or hydrogenolysis. The stoichiometric application can be divided into two categories; chiral auxiliary, where a new chiral center is created by the influence of the neighboring chiral group derived from hydrobenzoin; and chiral reagent, where a new chiral center is provided directly from hydrobenzoin.

3.1.1. Chiral auxiliary.

3.1.1.1. Asymmetric addition by carbon nucleophile. Asymmetric 1,2- or 1,4-addition by a carbon nucleophile can be conducted by the stereochemical effect of chiral hydrobenzoin, which is induced on the neighboring group of the reaction center. This chemistry was explored by Konopelski[53] and Jung[54] in the 1990s. Hydrobenzoin is generally introduced as a ketal moiety and removed after the completion of the reaction.

Mangeney reported that acetals derived from cyclohexene or cyclopentene carboaldehydes reacted with phenyl copper and boron trifluoride regio- and diastereoselectively. Chiral cyclohexane carboaldehyde was obtained in 92% ee (Scheme 14).[55]



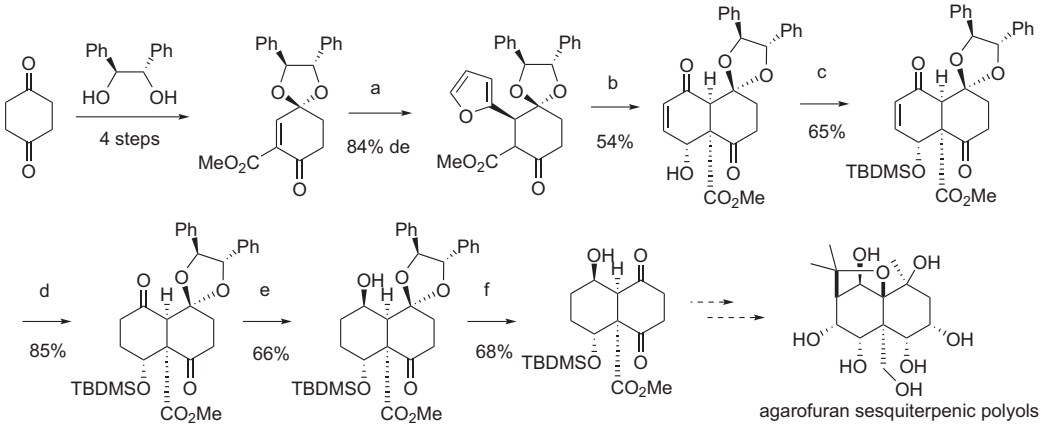
Scheme 14. Asymmetric addition of phenyl copper to cyclohexene aldehyde derivative.[55]

Ducrot utilized the hydrobenzoin-controlled asymmetric 1,4-addition of furane in the synthesis of the chiral decaline structure.[56] He optimized the reaction conditions and found that the desired isomer was obtained with 84% diastereomeric excess by cryogenic condition. Subsequent dimethyldioxirane-mediated oxidative ring opening of the furan yielded a chiral decaline. This is a precursor of agarofuran sesquiterpenic polyols, which attract attention with their antifeedant activity (Scheme 15).

Charette synthesized orthoacylimine bearing hydrobenzoin as chiral auxiliaries and tested the nucleophilic addition of organolithium reagents to imines.[57] The precursors can be prepared by an aza-Wittig reaction between the corresponding orthoacyl azide and a variety of aldehydes in the presence of trialkylphosphines. The nucleophilic addition of organolithium reagents led to the addition products in good yield and with good-to-excellent diastereoselectivity (from 85/15 to 99/1, Scheme 16).

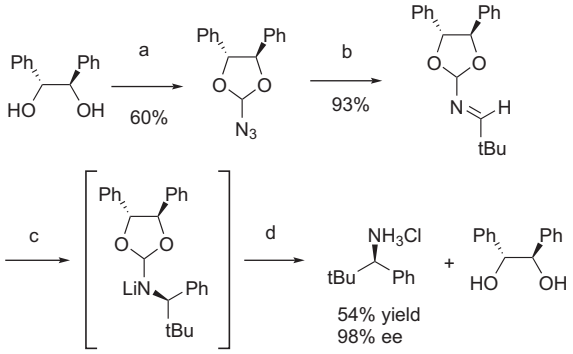
In the asymmetric aldol reaction, it is generally difficult to obtain *anti*-diol from the reaction of glycolate with aldehyde. If glycolate is in a fixed *E*-conformation by cyclization, an *anti*-selective aldol reaction can occur. Andrus reported that oxapyrone boron enolate, derived from chiral hydrobenzoin, underwent an *anti*-selective aldol reaction.[58] Deprotection by hydrogenolysis yielded chiral dihydroxyacid (Scheme 17).

3.1.1.2. Asymmetric Strecker synthesis. Metabotropic glutamate receptors (mGluRs) have attracted considerable attention as the lead compound for a wide range of central nervous disorders, such as Parkinson's disease and Alzheimer's disease. As the lead structure for a mGluR2/3 agonist, some groups have found a glutamic acid



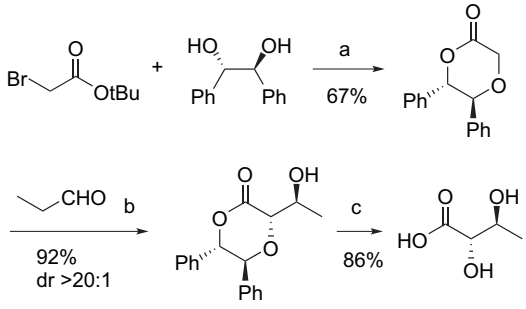
Reagents: a) Furane, BF_3-Et_2O; b) dimethyldioxirane; c) TBDMSOTf, 2,6-lutidine; d) H_2, Pd/C e) LTBA, THF; f) H_2, $Pd(OH)_2$/C

Scheme 15. Enantioselective synthesis of a key decalinic intermediate of agarofuran antifeedants.[56]



Reagents: a) 1) $HC(OMe)_3$, p-TsOH, 2) $TMSN_3$; b) tBuCHO, PMe_3, THF;
c) PhLi, DME; d) HClaq, MeOH

Scheme 16. Asymmetric addition of organolithium to imines bearing chiral hydrobenzoin auxiliaries.[57]



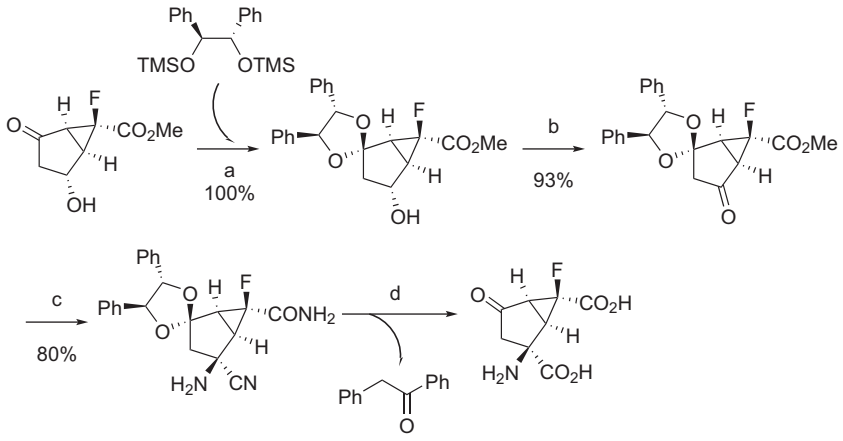
Reagents: a) n-Bu_2SnO; b) CH_3CH_2CHO, Et_3N, c-Hex_2BOTf, CH_2Cl_2;
c) H_2, Pd/C

Scheme 17. *anti*-Selective glycolate aldol addition with an oxapyrone boron enolate.[58]

whose formation is fixed by a bicyclo[3.1.0]hexane skeleton and have tried to develop an efficient synthetic route. One of the key steps is to determine how to construct a chiral amino acid on a five-membered ring. With regard to the asymmetric Strecker synthesis for preparing the amino acid moiety of MGS-0028, Yasuda examined the introduction of chiral protecting groups to neighboring carbonyl groups and found that (*S*,*S*)-hydrobenzoin was the best chiral auxiliary for asymmetric induction at the β-position carbonyl group (Scheme 18).[59] The desired amino nitrile was obtained after deprotection by acid treatment. During this treatment, hydrobenzoin from the ketal moiety was converted into benzyl phenyl ketone; this ketone was then easily separated by extraction.

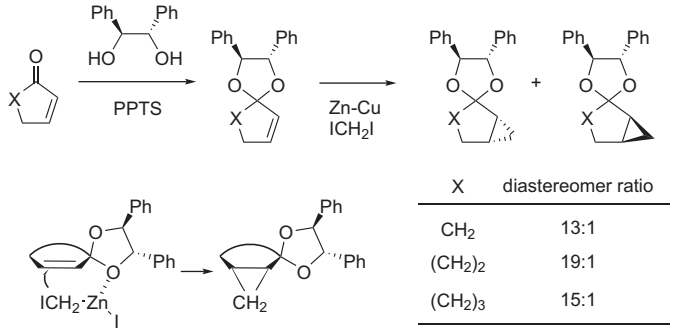
3.1.1.3. Asymmetric cyclopropanation. In 1989, Mash reported that 2-cycloalken-1-one (*S*,*S*)-hydrobenzoin ketal underwent efficient and highly diastereoselective cyclopropanation by treatment with an excess amount of the Simmons–Smith reagent. For example, 2-cyclohexen-1-one (*S*,*S*)-hydrobenzoin ketal gave an 87–90% yield of a crystalline mixture of diastereomeric norcaranone ketal in a 19/1 ratio. One recrystallization of this mixture provided diastereomerically pure compound.[60] A mechanistic study showed that diastereoselectivity was thought to result from preferential chelation of the Simmons–Smith reagent at the sterically hindered lone pair of electrons on the oxygen of hydrobenzoin (Scheme 19).

Asymmetric cyclopropanation can be used as the methylation to an enone in combination with the ring opening reaction. Cossy found that the photoreduction of alkyl-substituted bicyclo[4.1.0] heptanones with triethylamine leads to the corresponding 3-methylcycloalkanones. He applied this reaction to the synthesis of (+)-Ptilocaulin, the natural product that displays antimicrobial activity.[61] (*R*,*R*)-Hydrobenzoin was introduced to a cyclohexenone derivative by ketalization, following the Simmons–Smith reaction, giving chiral cyclopropane with 92% diastereomeric excess (Scheme 20). Irradiation of cyclopropyl ketone in acetonitrile in the



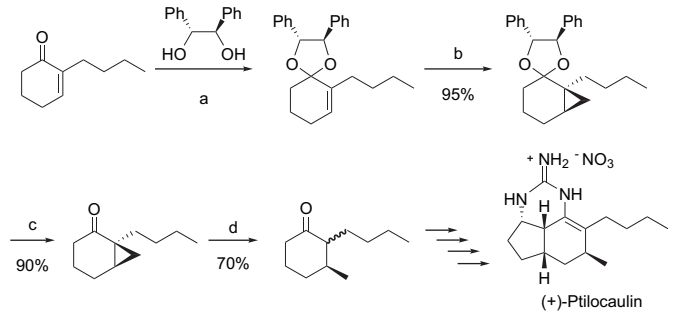
Reagents: a) TfOH, CH_2Cl_2; b) NaClO, $RuCl_3$; c) NH_3/MeOH, $Ti(OiPr)_4$, TMSCN; d) HCl, AcOH

Scheme 18. Asymmetric Strecker synthesis to prepare amino acid moiety of MGS-0028.[59]



X	diastereomer ratio
CH_2	13:1
$(CH_2)_2$	19:1
$(CH_2)_3$	15:1

Scheme 19. Asymmetric cyclopropanation of 2-cycloalken-1-one hydrobenzoin ketals.[60]



Reagents: a) PPTS; b) Zn-Cu, ICH_2I; c) HCl; d) light, NEt_3, $LiClO_4$

Scheme 20. The synthesis of (+)-Ptilocaulin via asymmetric cyclopropanation.[61]

presence of triethylamine led to the desired chiral methyl ketone. The epimerization was unavoidable, however; the mixture of epimers was converted into (+)-Ptilocaulin.

Cyclopropane rings also can be opened by Birch reduction. Cuparene is a sesquiterpene, which possesses adjacent quaternary centers in a cyclopentane ring, and has frequently been a target for enantioselective synthesis. Mash used asymmetric cyclopropanation using (*R*,*R*)-hydrobenzoin in the construction of a quaternary center of (*S*)-Cuparene. The resulting cyclopropane ring is opened by Li/ammonia to give the Cuparene structure (Scheme 21).[62]

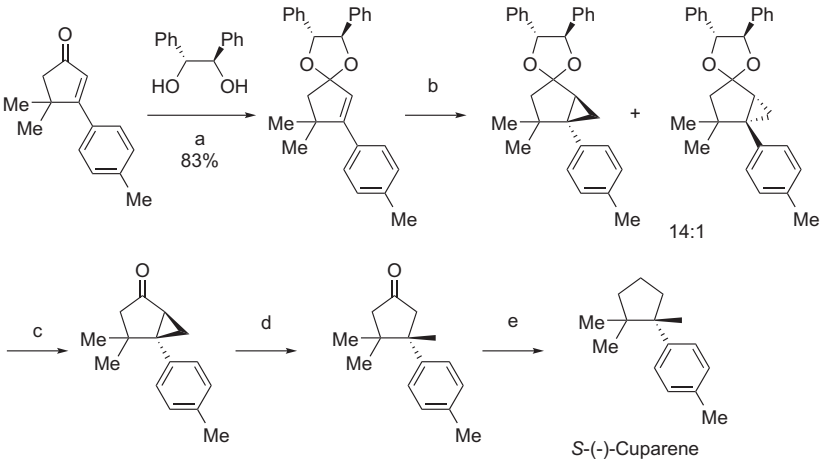
The ring opening reaction by trimethylsilyliodide affords a halomethyl group and can be utilized for the introduction of a side chain group having a chiral center. Corbett reported the asymmetric cyclopropanation of cyclopentenone, which afford an iodomethyl compound by following ring opening. This intermediate is utilized in the synthesis of glucokinase activators (Scheme 22).[63]

3.1.1.4. Asymmetric aziridination. Though asymmetric aziridination can be used as the enantioselective addition of an amino group to an olefin group as well as cyclopropanation, the chiral auxiliary method by hydrobenzoin has not achieved high selectivity. Tardella reported that the reaction of *N*-[[(4-nitrophenyl) sulphonyl]-oxy]carbamate with enol ether bearing chiral hydrobenzoin gave 2-(ethoxycarbonylamino)cyclohexanone as the main product; however, selectivity was at a modest level.[64] In a similar manner, asymmetric aziridination at the γ-position from the ketal was also reported[65] (Scheme 23).

3.1.1.5. Asymmetric cycloaddition. Asymmetric cycloaddition enables to control the stereochemistry of two chiral centers in one step. Diene, modified by hydrobenzoin, had been already applied to an asymmetric Diels–Alder reaction in 1989 by Konopelski.[66] Vinylketene acetal, derived from chiral hydrobenzoin, gave Diels–Alder adducts with moderate selectivity. Wallace examined heterodiene cycloaddition of 3-formyl chromone with ketene acetals modified by hydrobenzoin.[67] Acid-catalyzed methanolysis of the Diels–Alder adduct induces transesterification and retro-Claisen deformylation, generating chromone that has methylenecarboxylic acid introduced, releasing the hydrobenzoin to be regenerated. In 2003, Wallace applied a similar strategy to heterodyne, bearing an amino group, in order to obtain β-amino acid. The reaction of the aminomethylene carbonyl compounds and the chiral ketene acetal derived from hydrobenzoin gave cycloadducts with a high diastereoisomeric ratio (>19/1). The cycloadducts were similarly transformed into β-amino acid derivatives; however, the stereochemistry of the C2-position was not controlled[68] (Scheme 24).

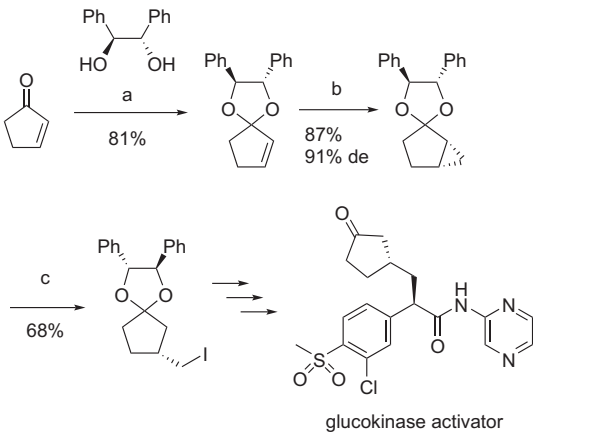
Stereoselective Diels–Alder reactions can occur by connecting diene and dienophile with a 1,2-diphenyl ethylene backbone, derived from chiral hydrobenzoin. Jung reported that an intramolecular Diels–Alder reaction proceeded diastereoselectively and formed chiral ketones in good yield[69] (Scheme 25).

By using the acrylate ester of both hydroxyl groups of hydrobenzoin as dienophile, 2 mol of Diels–Alder adducts can be obtained simultaneously. The requisite bis-acrylate was prepared by esterification of (*R*,*R*)-hydrobenzoin with acryloyl chloride.



Reagents: a) PPTS; b) CH_2I_2, Et_2Zn; c) 10% HClaq; d) Li/NH_3; e) Na/NH_2NH_2

Scheme 21. The synthesis of (−)-Cuparene via asymmetric cyclopropanation.[62]



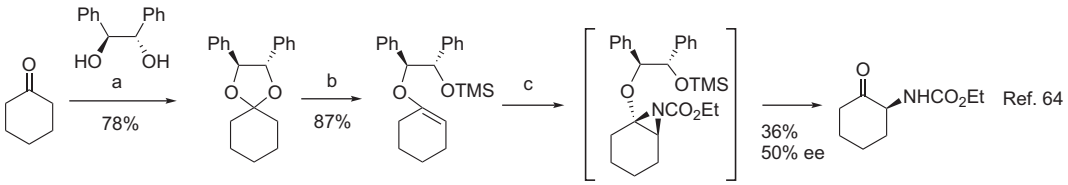
Reagents: a) Pyridinum *p*-toluenesulfonate, cyclohexane; b) Et_2Zn, $ClCH_2I$, EDC; c) TMSI, K_2CO_3, dioxane

Scheme 22. The synthesis of glucokinase activators via asymmetric cyclopropanation.[63]

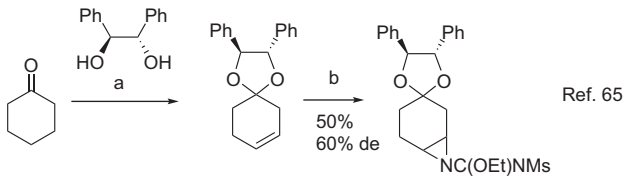
Addition of 1,3-butadiene to the crude acrylate in the presence of titanium tetrachloride, proceeded to form the bis-adduct in high yield. Saponification with lithium hydroxide in aqueous methanol gave an acid of 95% ee[70] (Scheme 26).

As the method of construction of the *C*-ring of steroid, a Diels–Alder reaction between diene and dienophile, which are connecting to hydrobenzoin together is reported. Shea prepared (+)-adrenosterone by an intramolecular Diels–Alder reaction between diene and dienophile, linked to (*S*,*S*)-hydrobenzoin.[71] When ethylene linkage was used, an unfavorable isomer was mainly obtained; however, (*S*,*S*)-hydrobenzoin auxiliary was found to be reversed the π-facial stereoselectivity of the ring closure (Scheme 27).

3.1.1.6. Asymmetric ene reaction and Pauson–Khand reaction. Asymmetric intramolecular cyclization of an enynyl compound is an important methodology for the construction of chiral polysubstituted cyclopentane, which is useful in the synthesis of natural compounds. Sato reported titanium(II)-mediated asymmetric intramolecular cyclization of 2,7-enynyl chiral acetals derived from hydrobenzoin.[72] The stereochemistry was controlled by

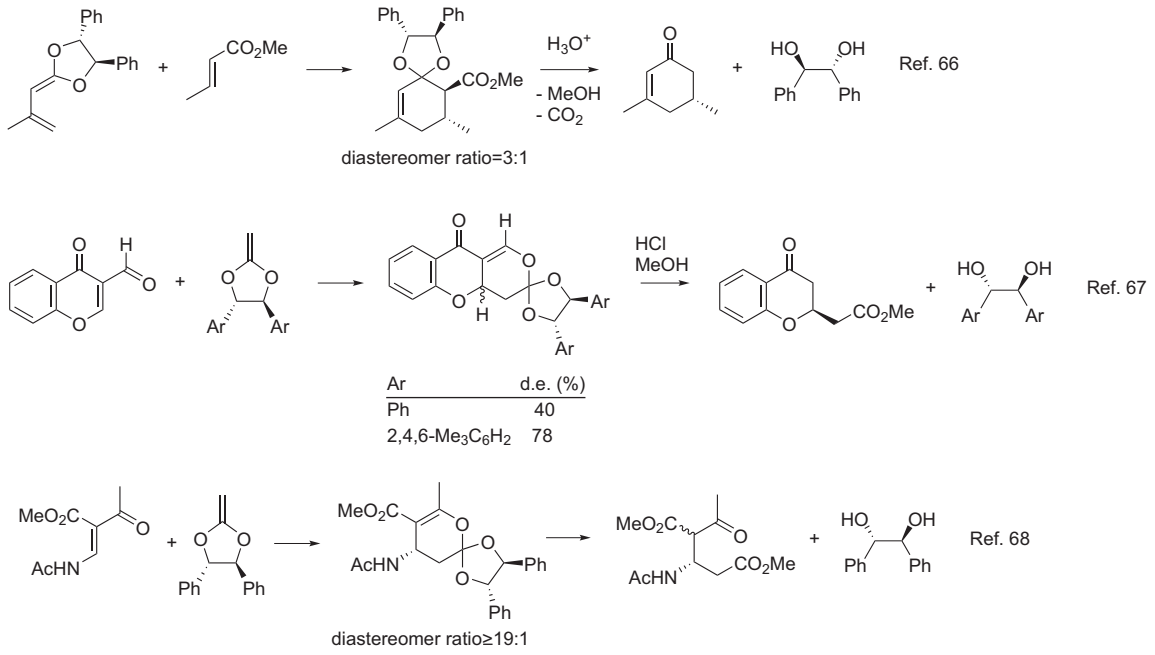


Reagents: a) Pyridinum *p*-toluenesulfonate; b) TfOTMS, ethyldiisopropylamme; c) N-[[(4-nitrophenyl)sulphonyl]-oxy]carbamate, triethylamine, CH_2Cl_2

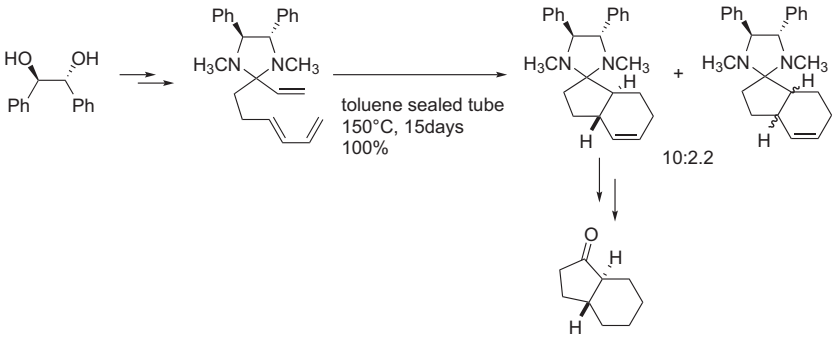


Reagents: a) TsOH, Benzene, b) $N_3C(OEt)NMs$, CH_2Cl_2

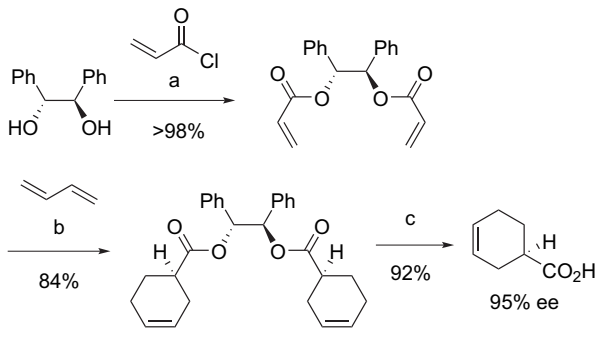
Scheme 23. Asymmetric aziridination of hydrobenzoin ketals.



Scheme 24. Asymmetric cycloaddition of ketene acetals derived from chiral hydrobenzoin.



Scheme 25. Asymmetric intramolecular Diels–Alder reaction.[69]



Reagents: a) Et_3N; b) $TiCl_4$, CH_2Cl_2, recryst. ; c) LiOH, MeOH, H_2O, rt

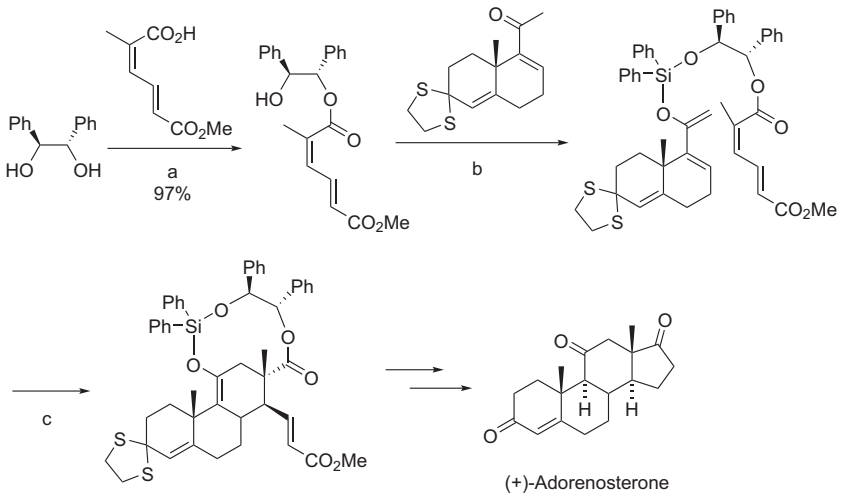
Scheme 26. Asymmetric Diels–Alder reaction with bis-acrylate of hydrobenzoin.[70]

a chiral hydrobenzoin acetal on the end of an ene group and synthesized cyclopentane derivatives, which can be readily transformed into a bicyclo[3,3,0]oct-1-en-3-one derivative. This is a useful intermediate for the synthesis of cyclopentanoid natural products, such as triquinanes (Scheme 28).

A chiral hydrobenzoin auxiliary on the trimethylene group also can control ene–yne cyclization. Meijere reported that a cyclopropylidenalkyne with a C_2-symmetric acetal moiety next to the triple bond underwent an asymmetric Pauson–Khand reaction and gave bicyclo[3,3,0]oct-1-en-3-one in one step[73] (Scheme 29).

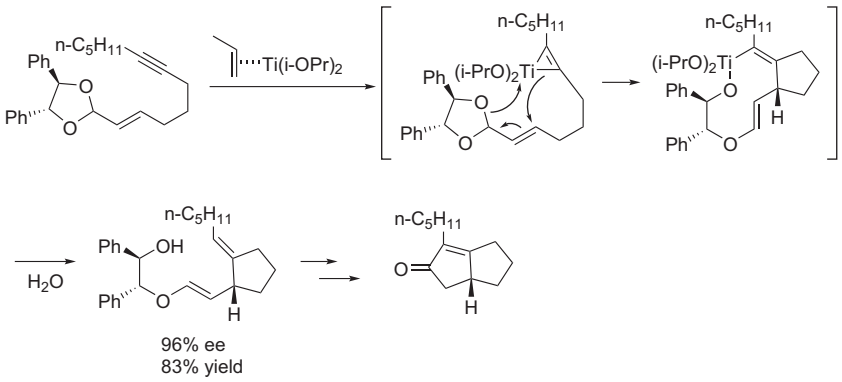
3.1.1.7. Asymmetric reduction. α-Ketoacid is still a tough substrate in the catalytic asymmetric reduction of ketones. Though heterogeneous chiral catalysts give good enantioselectivity for α-keto acid, heterogeneous chiral catalysts are generally not available in industrially. The diastereoselective reduction of α-keto esters bearing chiral alcohol, which stem from Prelog's historical work, still has practical value. Rosini reported that α-ketoester, prepared in three steps from chiral hydrobenzoin, can be reduced by several agents, providing the corresponding α-hydroxyester with medium diastereoselectivity. This selectivity has been interpreted as being due to carbonyl face-shielding by the stacking benzyl moiety and hydrobenzoin[74] (Scheme 30).

3.1.1.8. Asymmetric protonation. Enantioselective protonation of a prostereogenic center is conceptually simple and has been shown to be an attractive route for the preparation of enantiomerically pure compounds. The majority of these reports use a stoichiometric amount of the chiral proton source to a stereochemically labile

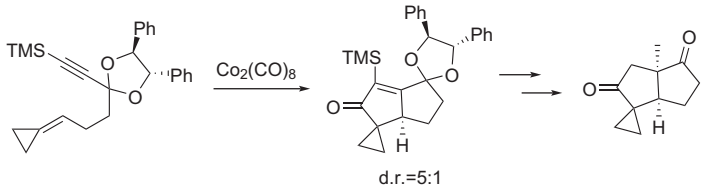


Reagents: a) i) oxalyl chloride, DMF, CH_2Cl_2, ii) NEt_3, CH_2Cl_2, b) i) KHMDS, THF, -78 °C, 2 h; ii) Ph_2SiCl_2, NEt_3, 0 °C, 30min; iii) DMAP, 0 °C, c) toluene, 200 °C, 18 h,

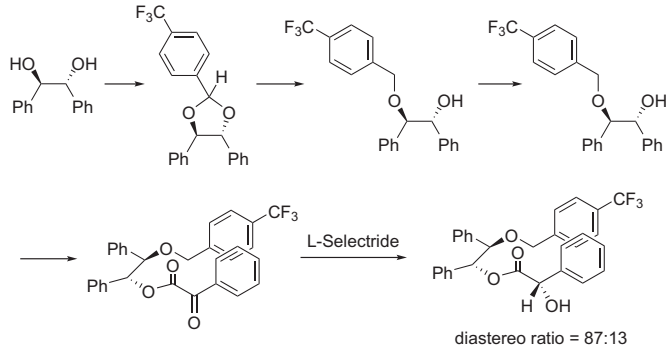
Scheme 27. Hydrobenzoin assisted asymmetric Diels–Alder reaction.[71]



Scheme 28. Hydrobenzoin assisted intramolecular asymmetric metallo-ene reaction.[72]

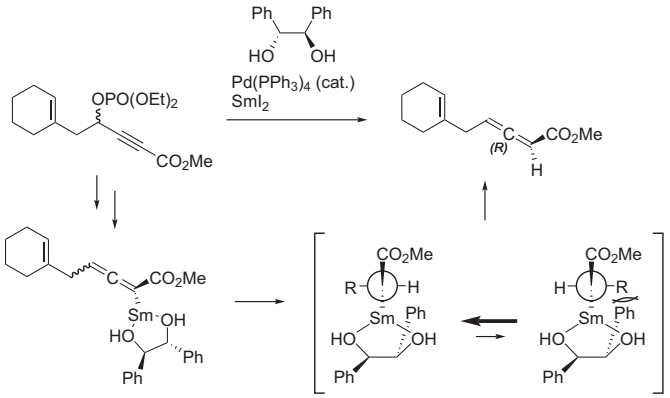


Scheme 29. Hydrobenzoin assisted intramolecular Pauson–Khand reaction.[73]



Scheme 30. Asymmetric reduction of α-keto acid using hydrobenzoin as chiral auxiliary.[74]

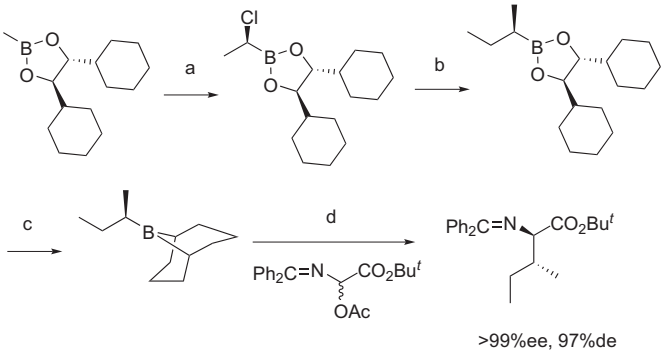
proton acceptor. Notably Lewis acidic samarium (III)-mediated enantioselective protonation propargylic phosphates is used in the synthesis of chiral allenic esters. Chiral allenic esters are valuable intermediates of natural products. In this reaction, reduction proceeds by proton transfer from an alcohol coordinating on samarium. Mikami found that SmI_2-mediated reduction of propargylic phosphates proceeded with racemization and that carbanionic samarium (III) species are racemized via a propargylic intermediate. He applied this finding to the dynamic kinetic resolution of racemic propargylic phosphates and found that highly enantio-enriched allenic ester was obtained by using hydrobenzoin as a chiral proton source in this system[75] (Scheme 31).



Scheme 31. Dynamic kinetic protonation of propargyl ester using chiral hydrobenzoin.[75]

3.1.1.9. Asymmetric insertion. Boronic esters have two alkoxy groups and a reactive alkyl group; therefore, it is possible to control stereoselectivity of the reaction of boronic ester by chiral diol on the boron atom. Matteson examined asymmetric chloromethylene insertion of boronic esters bearing chiral diols and showed that 1,2-dicyclohexyl-1,2-ethanediol (DICHED), derived from hydrobenzoin, is a good controller for this reaction (Matteson reaction).[76] DICHED is prepared from catalytic hydrogenation of 2-methoxy-4,5-diphenyl-1,3,2-dioxaborolane. He synthesized the precursor of Stegobiol, pheromones of the beetle, by repeated asymmetric insertion reaction of the chloromethylene group[77] (Scheme 32).

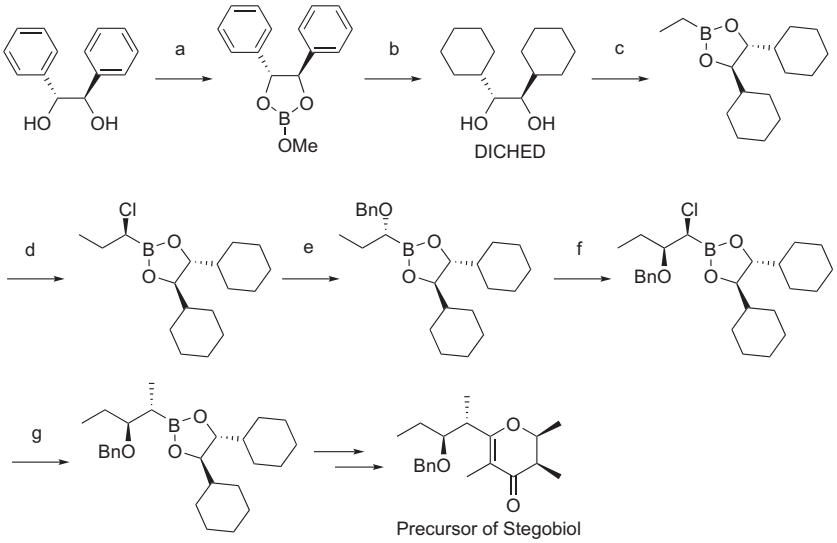
O'Donnell found the Matteson reaction is useful for the synthesis of the intermediate in the stereoselective boron alkylation reaction that they developed for asymmetric synthesis of β-substituted α-amino acid[78] (Scheme 33).



Reagents: a) $LiCHCl_2$, $ZnCl_2$, b) EtMgBr, c) 1) LAH, 2) COD, d) cinchonine, nBuLi, LiCl, THF

Scheme 33. Synthesis of β-substituted α-amino acid by Matteson reaction.[78]

3.1.1.10. Asymmetric reaction of chiral p-benzoquinone. March synthesized a chiral monoketal derived from *p*-benzoquinone and hydrobenzoin and established its usefulness in the various steric controls on the chiral cyclohexane ring.[79] Partial hydrogenation of the monoketal by Wilkinson's catalyst and following reduction with sodium borohydride and deprotection with montmorillonite K-10 gives chiral 4-hydroxy-2-cyclohexenone,[80] which has been used as a building block in the synthesis of the *anti*-cholesterol agents Compactin and ML-236A and the immunosuppressant FK-506. On the other hand, intramolecular cyclization on the cyclohexane ring is also controlled by a hydrobenzoin ketal unit. Treatment of the monoketal with ethyl iodoacetate in the presence of indium powder gave ester. The following reduction by lithium borohydride gave the alcohol of a benzofuran precursor. An intramolecular addition of the primary alcohol to the olefin could give rise to up to four diastereoisomers, but the stereochemical circumstance of ring closing reactions leading to benzofurans only gave cis fused isomers conveniently. Furthermore,



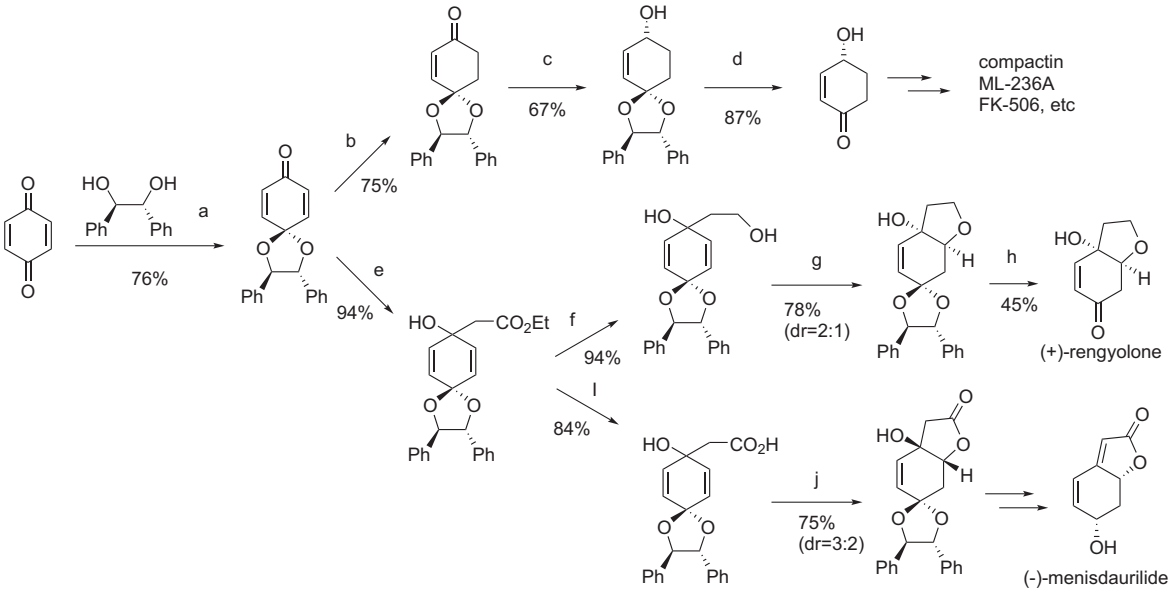
Reagents: a) $B(OMe)_3$; b) 1) H_2/Rh, 2) NaOH, $C(CH_2OH)_4$; c) $EtB(OBu)_2$; d) $LiCHCl_2$, $ZnCl_2$; e) BnOLi; f) $LiCHCl_2$, $ZnCl_2$; g) MeMgBr

Scheme 32. Asymmetric insertion of methylene group assisted by DICHED.[77]

the enantioselective ring closing reaction with mercuric trifluoroacetate, followed by reduction with sodium borohydride, afforded a ca. 2/1 enantiomer mixture of chiral benzofuran. Removal of the chiral hydrobenzoin from the major stereoisomer using montmorillonite K-10 yielded (+)-rengyolone. In a similar fashion, γ-lactonization was achieved by intramolecular addition of the carboxylic acid to the olefin, promoted by trifluoroacetic acid. The cis fused lactone was isolated and transformed to (−)-menisdaurilide (Scheme 34).[81]

an oxygen source and chiral controller. In this section, reactions of this type are summarized, in distinction from the usual chiral auxiliary.

Fujioka has explored the various applications of chiral hydrobenzoin, obtained from asymmetric synthesis, based on the nucleophilicity of the oxygen atom. In 1996, Fujioka reported that chiral 1,4- and 1,5-diols can be synthesized from en-acetal, that is, prepared from the corresponding aldehyde and hydrobenzoin; in

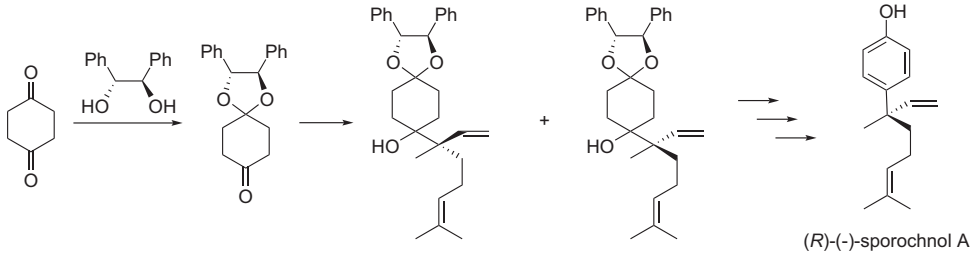


Reagents: a) HCl, b) H_2, $RhCl(PPh_3)_3$, c) $NaBH_4$, d) montmorillonite K-10, e) ICH_2CO_2Et, In powder, f) $LiBH_4$, g) $Hg(CF_3COO)_2$, $NaBH_4$, NaOH, h) montmorillonite K-10, CH_2Cl_2, i) KOH, j) CF_3CO_2H

Scheme 34. Asymmetric transformations from chiral ketal derived from *p*-benzoquinone and hydrobenzoin.[79–81]

Similarly, Busque reported the asymmetric transformation of 1,4-cyclohexanedione monoketal, bearing hydrobenzoin. Unfortunately, enantioselective reaction was not observed in the alkylation of the chiral monoketal. Separation of the diastereomer by the repeated crystallization successfully gave an enantiopure intermediate. It was transformed to (*R*)-(−)-sporochnol, which has been found to show significant feeding deterrence toward herbivorous fishes[82] (Scheme 35).

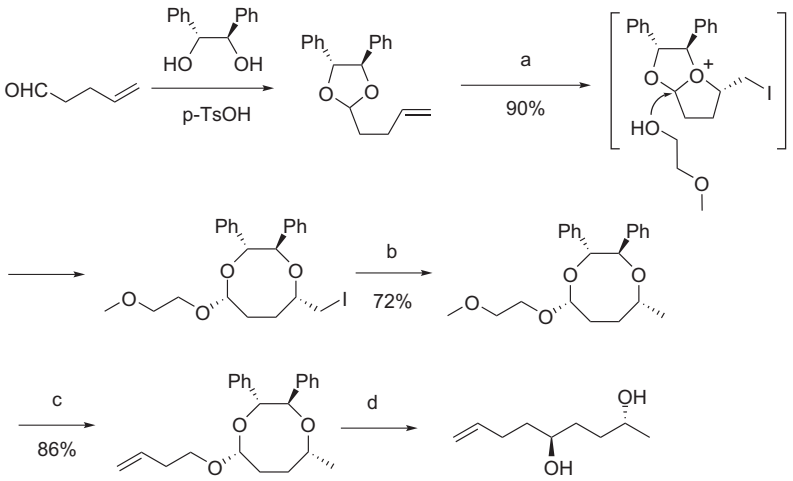
this case, remote asymmetric induction is the key step.[83] The key step of Fujioka's chemistry is the stereoselective formation of an oxonium intermediate, fused with two five-membered rings, and the following stereoselective attack of alkoxide, which gives eight-membered cyclic ether, comprising chiral hydrobenzoin. The stereoselectivity of both steps is controlled by chiral hydrobenzoin. When methoxyethyl group is introduced, the nucleophilic replacement of the alkoxy group by Grignard reagents at the acetal



Scheme 35. Asymmetric synthesis of sporochnol from chiral cyclohexane monoketal.[82]

3.1.2. Chiral reagent. The oxygen of hydrobenzoin has nucleophilicity toward electrophilic carbons. By utilization of these characteristics, a new oxygen functional group can be introduced on the prochiral carbon from chiral hydrobenzoin, which is accompanied with chiral transfer. A diphenylethylene group can be easily removed by hydrogenolysis to leave the oxygen. In this type of reaction, hydrobenzoin plays two roles:

carbon occurs in good yields with complete retention. The reason for the good yields and complete retention of stereochemistry can be attributed to chelation of the methoxyethoxy group to magnesium. The chiral hydrobenzoin unit is easily removed by catalytic hydrogenolysis or Birch reduction. This reaction gives a general strategy for the synthesis of chiral 1,4- and 1,5-diols from an ene aldehyde (Scheme 36).

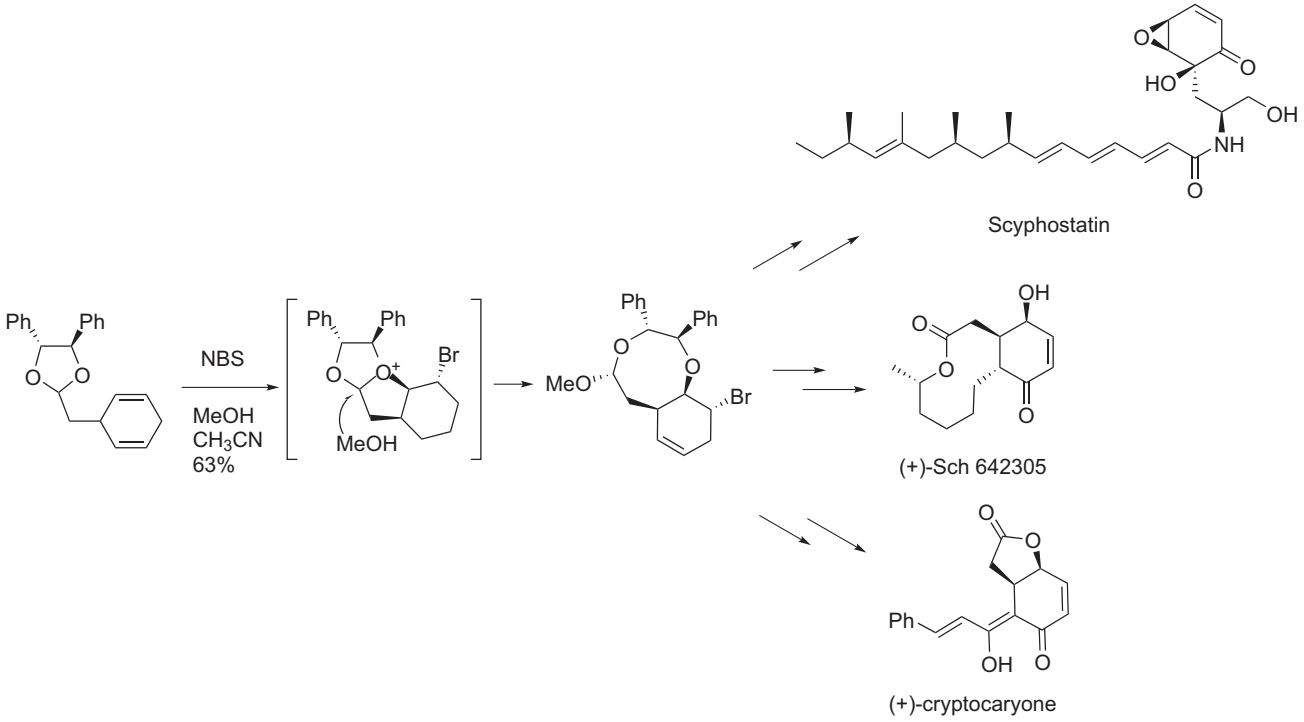


Reagents: a) $I(Coll)_2ClO_4$, $MeOCH_2CH_2OH$, CH_2Cl_2; b) $LiAlH_4$, THF; c) $CH_2=CHCH_2CH_2MgBr$, Toluene; d) Ca, NH_3

Scheme 36. Asymmetric synthesis of 1,4-diol via an intramolecular haloetherification reaction.[83]

Fujioka's reaction has wide capability for the various asymmetric syntheses of natural compounds. By using cyclohexadiene as the starting material, cyclohexene-fused eight-membered cyclic ether can be obtained. This compound can be used commonly as an intermediate for the synthesis of cyclohexene containing natural compounds, such as scyphostatin,[84] (+)-Sch 642305,[85] and (+)-cryptocaryone[86] (Scheme 37).

Cyclitols have recently attracted a great deal of attention due to their diverse biological activities and their versatility as synthetic intermediates. For example, D-*chiro*-inositol is considered to be one of the significant constituents of putative insulin mediators. Kim reported that a reaction of 3-bromocyclohexene with (*S*,*S*)-hydrobenzoin and subsequent intramolecular oxyselenenylation of the resulting allylic ethers, followed by oxidation–elimination, afford-

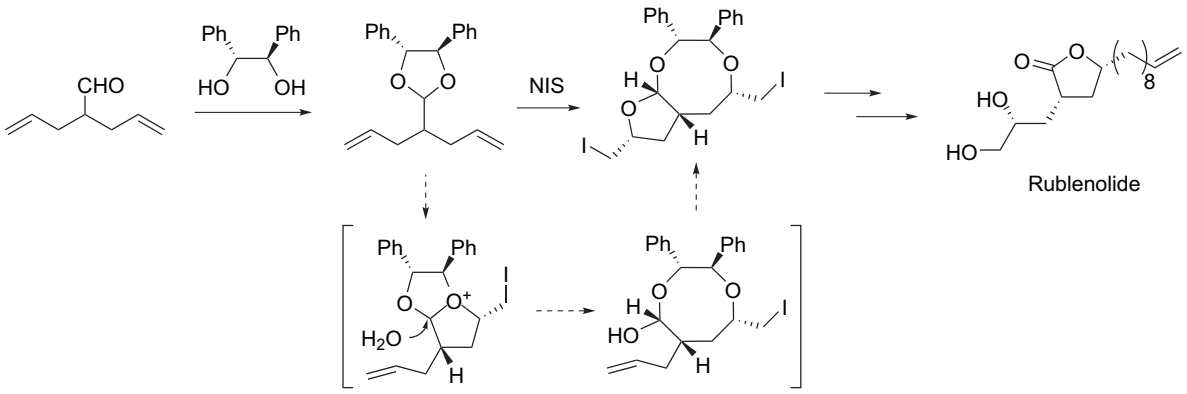


Scheme 37. Intramolecular bromoetherification of cyclohexadiene acetal.[84–86]

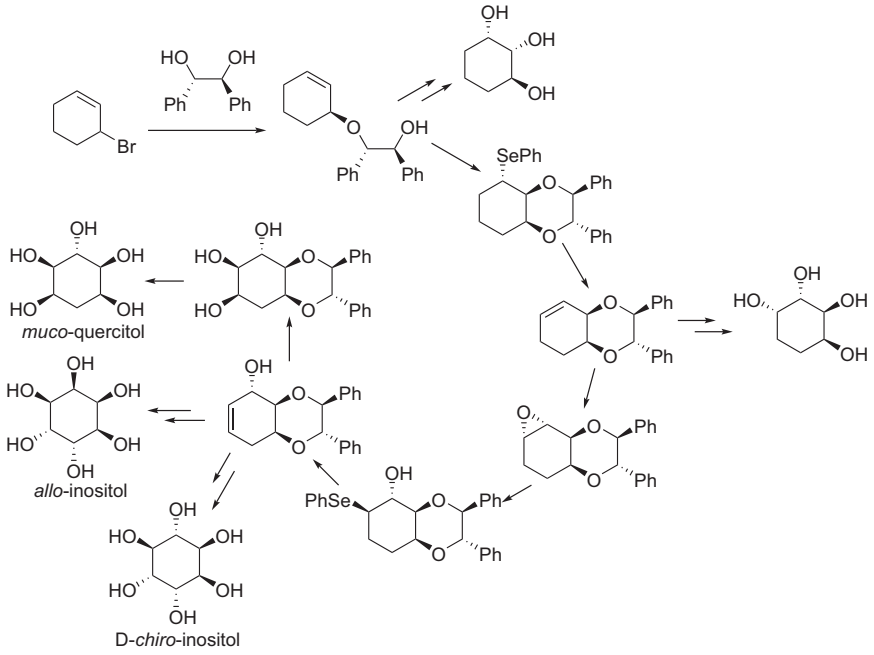
When σ-symmetric diene is used as the starting material, double intramolecular iodoetherification occurs and gives tetrahydrofuran-fused eight-membered cyclic ether in one pot. Four chiral centers of this compound are derived from a domino reaction controlled by chiral hydrobenzoin. Fujioka applied this chemistry to the synthesis of rubrenolide, a natural product that has been isolated from trunk wood of the Amazonian tree[87] (Scheme 38).

ded valuable *cis*-fused bicyclic olefins.[88] Further, stereoselective transformation of these *cis*-fused bicyclic olefins afforded the enantiopure cyclohexitol *muco*-quercitol, D-*chiro*-inocitol, and *allo*-inocitol. Chiral hydrobenzoin plays both roles of chirality control and an oxygen source (Scheme 39).

The chiral azide derived from hydrobenzoin can be used in an asymmetric Schmidt reaction. Aube showed that chiral



Scheme 38. Double iodoetherification of σ-symmetric diene acetals.[87]

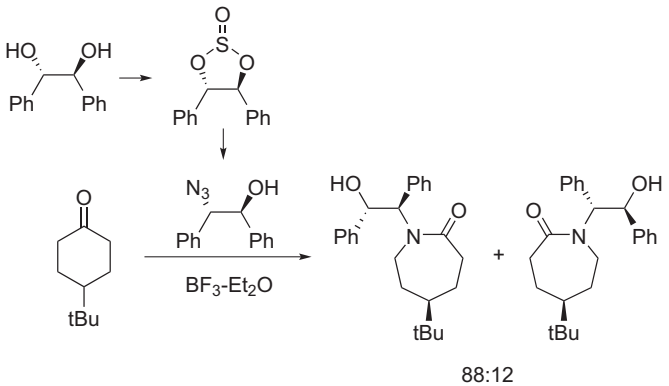


Scheme 39. Synthesis of enantiopure cyclitols by intramolecular oxyselenenylation.[88]

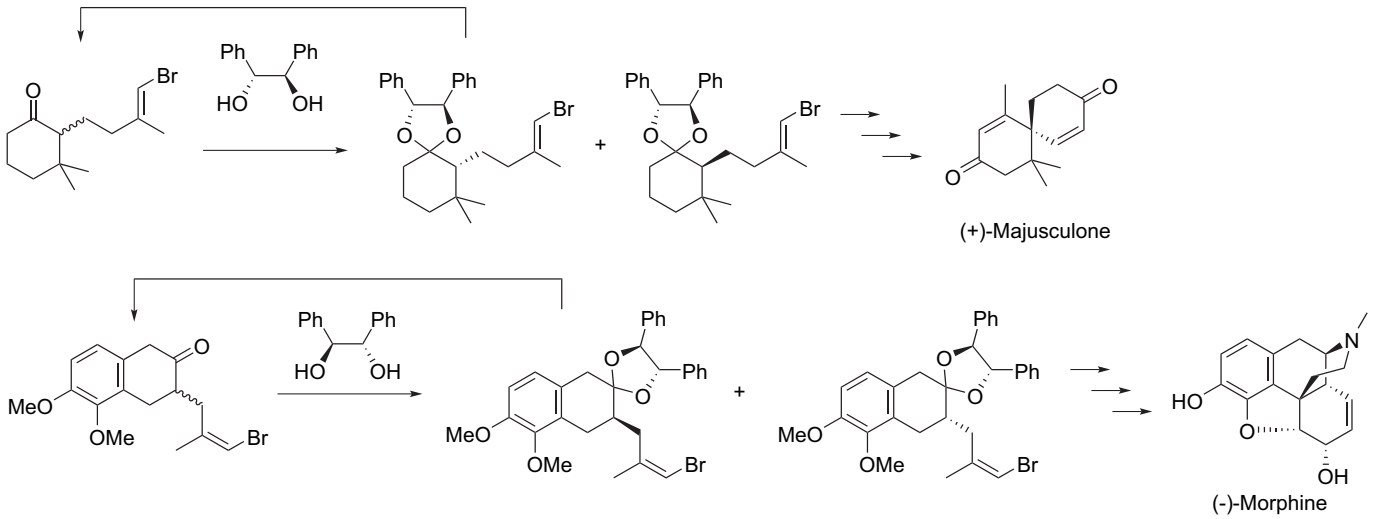
hydroxyalkyl azides react with cyclohexanones and afforded chiral lactam derivatives.[89] The highest selectivity was obtained by using monosubstituted 1,3-hydroxyalkyl azides; however, azide derived from hydrobenzoin showed the best result among monosubstituted 1,2-hydroxyalkyl azides (Scheme 40).

3.1.3. Chiral reagent for optical resolution. In the optical resolution of compounds that have ketones, separation of a diastereomer mixture of ketals derived from chiral diol is often used. Usually, column separation is used at the separation process. Taber used chiral hydrobenzoin in the optical resolution of α-alkylated cyclohexanone derivatives for the synthesis of (−)-morphine[90] and (+)-majusculone.[91] In both syntheses, undesired isomer was readily recovered by deprotection in acidic conditions (Scheme 41).

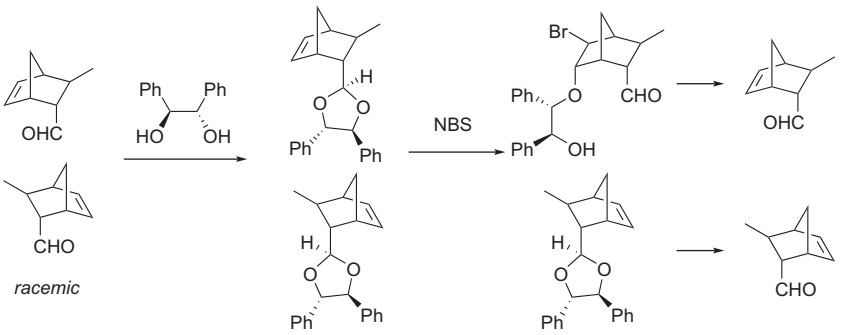
Separation using asymmetric desymmetrization by an intramolecular reaction in which chiral hydrobenzoin is used as a protecting group has been reported. Fujioka reported that a haloetherification reaction of a diastereomeric mixture of ene acetals, derived from racemic norbornene aldehydes and (*S*,*S*)-hydrobenzoin, proceeded in a kinetically controlled manner to give enantiopure, optically pure haloether.[92] Retrobromoetherification gave optically pure norbornene and chiral hydrobenzoin. Hydrobenzoin showed the best result in the commercially available chiral diols (Scheme 42).



Scheme 40. Asymmetric Schmidt reaction by chiral azides derived from hydrobenzoin.[89]



Scheme 41. Synthesis of (−)-morphine and (+)-majusculone by optical resolution using hydrobenzoin.[90,91]



Scheme 42. Asymmetric desymmetrization by intramolecular haloetherification.[92]

3.2. Catalytic application in asymmetric reactions

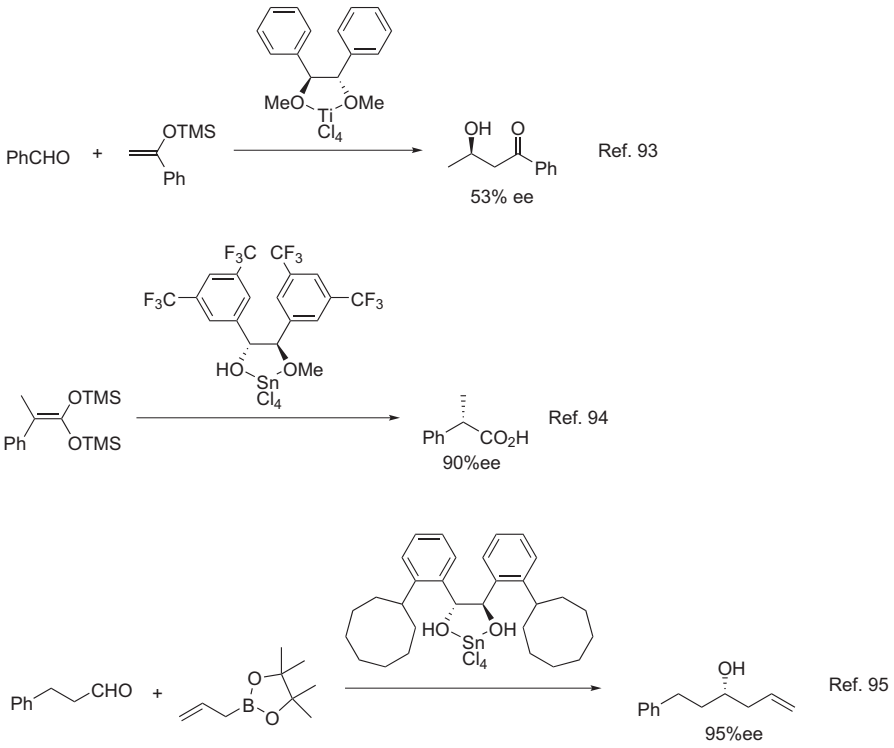
C_2-Symmetric bidentate compounds are frequently used as chiral ligands in asymmetric reactions. Whereas phosphine or nitrogen ligands are used with late-transition metals, oxygen ligands are often used with alkali metals, alkaline earth metals, and early-transition metals. This is due to the affinity of oxygen atoms to these groups of metals. Hydrobenzoin is one of the representative diols that are used as chiral ligands in asymmetric synthesis. In this section, the example of a catalyst (including nearly stoichiometric use) of chiral hydrobenzoin is summarized.

3.2.1. Asymmetric aldol-type reaction. The asymmetric aldol reaction has a long history of challenge and still has been a hot area in chiral chemistry. Various chiral catalysts, including organometal catalysts to organocatalysts, have been examined recently by many groups. Hydrobenzoin has also been applied as various forms in this reaction.

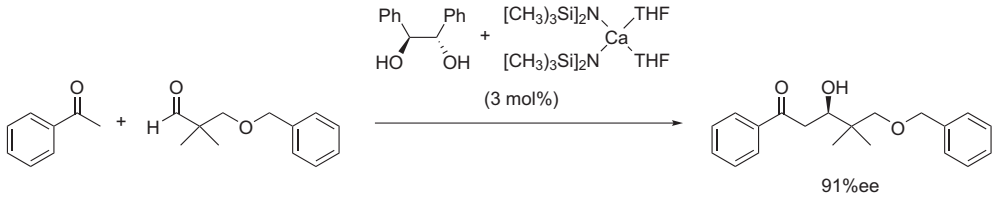
The applications of a Lewis acid complex with chiral hydrobenzoin derivatives are reported by several groups. As an early example, Akiba isolated six-coordinate titanium complexes from titanium tetrachloride and Tomioka ether (1,2-diphenylethane-1,2-diol dimethyl ether) and reported that cationic Lewis acid, generated from the complex, catalyzed an asymmetric aldol reaction with silyl enol ether; however, the enantiomeric excess was moderate level.[93] In 2003, Yamamoto found that monoalkyl ethers of hydrobenzoin catalyzed the enantioselective protonation of various silyl enol ethers in the presence of tin tetrachloride.[94] His concept is a Lewis acid-assisted chiral Brønsted acid (LBA) system; the coordination of Lewis acids with Brønsted acids restricts the orientation of protons, and increases their acidity. Recently, Hall reported that the combination of hydrobenzoin with tin tetrachloride under Yamamoto's concept led to high levels of asymmetric induction in the allylboration of aldehydes by allylboronic acid pinacol ester. The corresponding homoallylic alcohol products of synthetically useful aliphatic aldehydes are obtained in excellent yields with up to 96% ee by using *ortho*-cyclooctyl hydrobenzoin (Vivol) tin tetrachloride complex[95] (Scheme 43).

The direct catalytic asymmetric aldol reaction between unmodified ketones and aldehydes is highly desirable. Noyori reported the catalytic asymmetric aldol reaction of ketones and aldehydes using calcium alkoxides prepared from chiral hydrobenzoin.[96] A chiral hydrobenzoin/calcium complex catalyzes the reaction of acetophenone with aliphatic aldehydes to give the corresponding aldol products. This method facilitated the synthesis of chiral hydroxyketone in a 76% yield with 91% ee. This compound can be used as a synthetic intermediate for epothilone A, a new class of anti-tumor agents (Scheme 44).

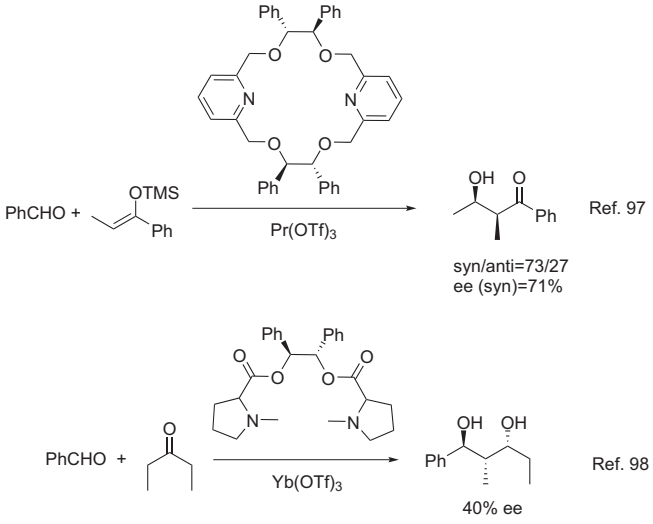
The combination of a hydrobenzoin derivative and rare metal has been examined by two groups. Kobayashi reported catalytic asymmetric aldol reactions using praseodymium triflate and chiral bis-pyridino-18-crown-6, which has a chiral diol unit.[97] Mlynarski also reported an asymmetric aldol-Tishchenko reaction, promoted by Ytterbium complexes with the chiral diol and diamine ligand.[98] In both case, hydrobenzoin is not the best ligand, however, the unique nature of the rare metal complex of the hydrobenzoin unit has been revealed (Scheme 45).



Scheme 43. Asymmetric aldol-type reaction by hydrobenzoin–early-transition metal catalysts.



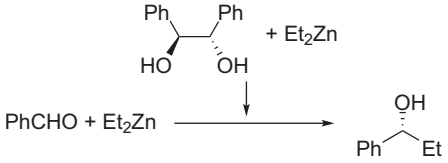
Scheme 44. Asymmetric aldol reaction by hydrobenzoin-calcium catalyst.[96]



Scheme 45. Asymmetric aldol reaction by hydrobenzoin–rare metal catalyst.

3.2.2. Asymmetric addition of diethyl zinc. The catalytic asymmetric addition of diethyl zinc to prochiral aldehyde has been usually developed employing β-amino alcohols or diamines as chiral ligands. In 1990, Salvadori reported the first example of the asymmetric addition of diethyl zinc promoted by chiral hydrobenzoin.[99] His method is mixing diethyl zinc to a solution of (*S*,*S*)-hydrobenzoin in toluene and stirring at room temperature. After cooling at 0 °C, aldehyde was introduced, and the homogeneous solution was stirred for 20 h at room temperature. The corresponding (*R*)-alcohol was obtained; however, a long reaction time was needed and the enantiomeric excess was modest level. Joshi estimated that Salvadori's catalyst was zinc monoalkoxide and improved the reactivity and enantiomeric excess by raising the temperature during catalyst formation (Table 7).[100] He stated that zinc dialkoxide was formed as an active catalyst; however, spectroscopic evidence of zinc dialkoxide was not presented.

Table 7
Asymmetric addition of diethyl zinc catalyzed by hydrobenzoin



Catalyst preparation	Time (h)	Yield (%)	ee (%)	Ref.
r.t., 30 min	69	99	77	99
80 °C, 30 min	18	98	89	100

Recently, Hitchcock reported mechanistic research of this reaction and proposed a transition state structure.[101] The stereochemical outcome of this reaction can be influenced by the addition of titanium isopropoxide. The enantiomeric ratios obtained in the absence of titanium isopropoxide favor the (*S*)-enantiomer, whereas the ratios obtained from the use of titanium isopropoxide favor the formation of the (*R*)-enantiomer. The formation of the opposite enantiomers is attributed to the different transition states mediated by either zinc or titanium (Scheme 46).

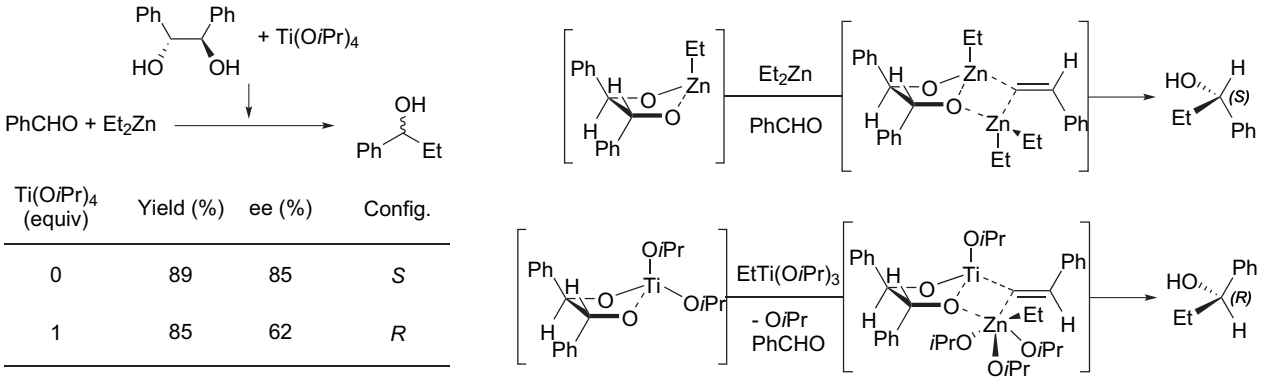
as a chiral ligand in the enantioselective conjugate addition of a phenyllithium to an α,β-unsaturated aldimine.[102] The Merck group used Tomioka ether as an additive in the enantioselective 1,4-addition of aryl lithium to produce α,β-unsaturated esters.[103] Generally, this reaction can be done in the presence of the catalytic amount of ligand; however, a stoichiometric amount of ligand is often used by the reason of reactivity. Tomioka applied this reaction to the synthesis of (−)-lycorine, the most abundant Amaryllidaceae alkaloid.[104] Tomioka ether forms a chelated complex with organolithium, where two methyl groups on the ether oxygen atoms are placed on the up and down faces of the five-membered chelate due to steric reasons, thus avoiding repulsion between the methyl group and the adjacent phenyl groups (Scheme 47).

When the 1,4-adduct of organolithium generates a carbanion, two chiral centers are constructed by the sequential reaction with the electrophile. Kündig used Tomioka ether in asymmetric 1,4-addition to an arene complexed to the electrophilic $Cr(CO)_3$ moiety and developed sequential the asymmetric addition of alkyl lithium and a electrophile to arene to give 1,2-*trans*-disubstituted dihydroarenes.[105] By this methodology, he achieved the synthesis of an enantiomer of 15-acetoxytubipofuran, cytotoxic sesquiterpenoid[106] (Scheme 48).

Bridged zirconocene, bearing a seven-membered ring, is a polymerization catalyst for an isotactic polypropylene developed in Mitsubishi Chemical. A silylene-bridged ligand was obtained by the addition of phenyllithium to 2-methylazulene, following silylation of the azulenyl anion. The *meso* form of the ligand, which obtained the combination of the enantiomer of the azulenyl anion, does not have polymerization activity; therefore, enantioselective addition of phenyllithium to azulene was examined to increase the ratio of the racemic form. We have applied Tomioka ether to the asymmetric synthesis of this ligand and obtained a modest enantiomeric excess of the bis-azulenyl ligand[107] (Scheme 49).

The enantioselective Michael reaction of a lithium ester enolate with enoate was also achieved by hydrobenzoin dimethyl ether.[108] This reaction is applied to synthesis of a halichlorine intermediate[109] (Scheme 50).

The conjugate addition reaction of lithium *N*-benzyltrimethylsilylamide with enoates is catalyzed by Tomioka ether to produce β-amino esters in high enantioselectivity up to 99% ee and



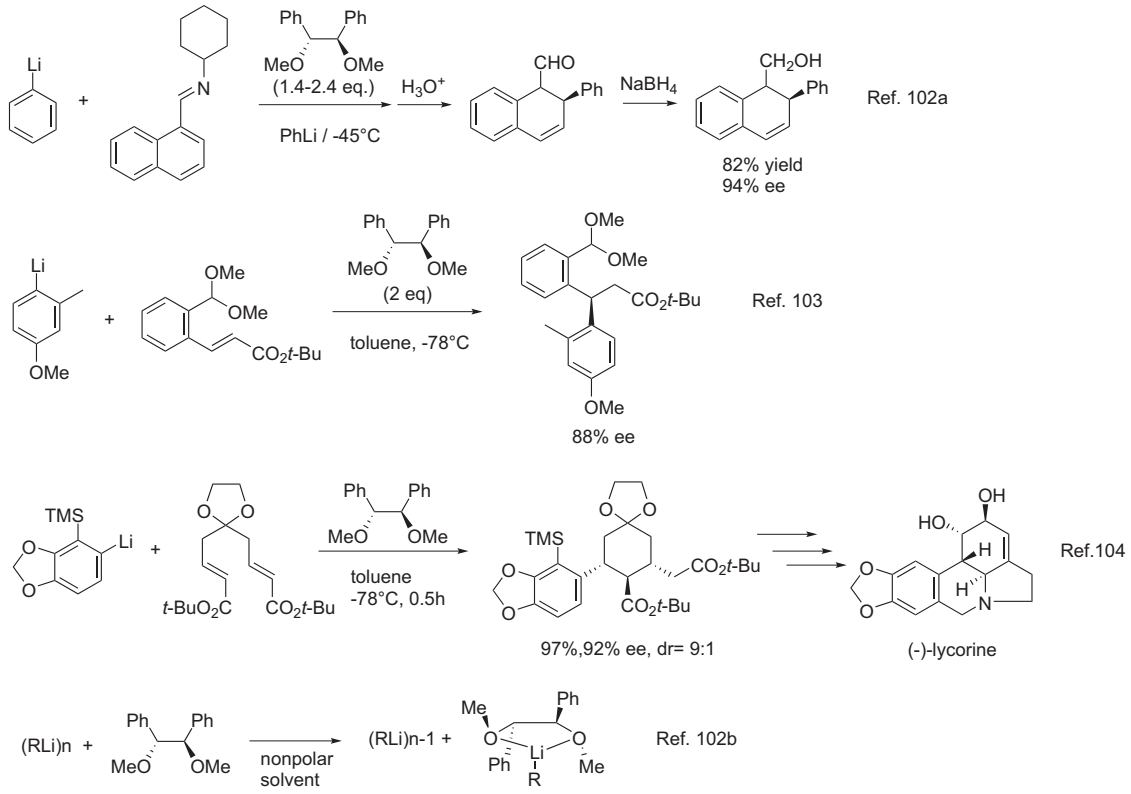
$Ti(OiPr)_4$ (equiv)	Yield (%)	ee (%)	Config.
0	89	85	*S*
1	85	62	*R*

Scheme 46. Effect of titanium isopropoxide in asymmetric addition of diethyl zinc.[101]

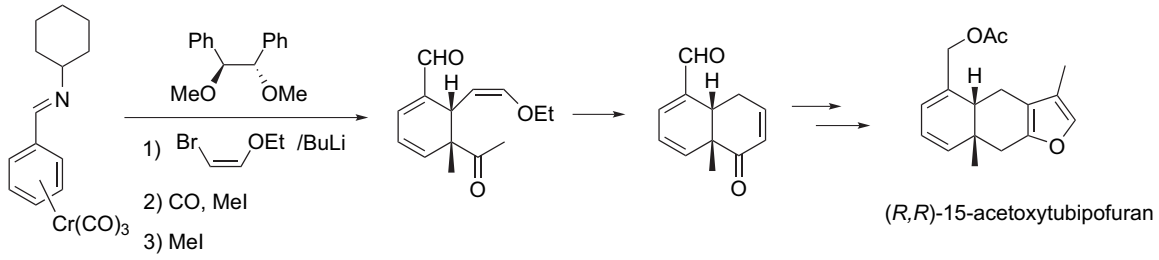
3.2.3. Asymmetric conjugate addition. The alkylation of oxygen of geminal diol gives a C_2-symmetrical diether, which is used as an external ligand in the enantio-control of organolithium reactions. This chemistry was mainly explored by Tomioka, and hydrobenzoin dimethyl ether is called 'Tomioka ether.' Coordination of ether oxygen to a lithium ion provides an effective chiral environment and enhances the reactivity. In 1989, Tomioka first reported that a stoichiometric amount of chiral Tomioka ether acts

high yields. This was the first example of an external chiral ligand-controlled, asymmetric conjugate addition of lithium amides to enoates.[110] This reaction is applied to the synthesis of (−)-aspidospermidine[111] (Scheme 51).

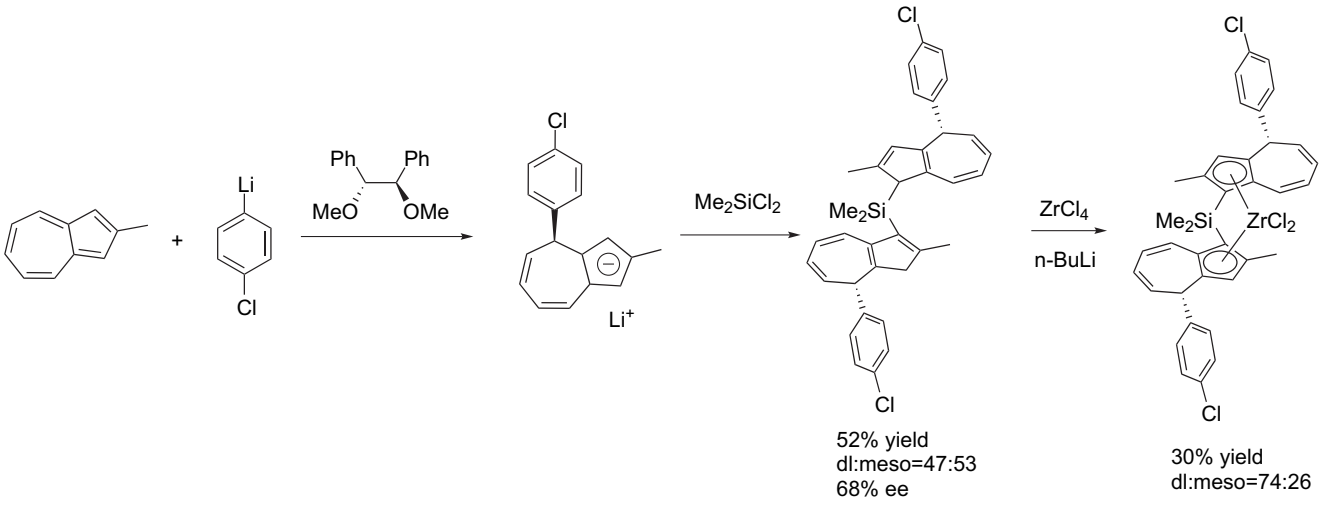
Chiral bisphosphazide is also examined as a functional group to coordinate to oragnolithium. Naka reported that chiral bisphosphazides present a possible application as a promising dual basic functionality (both a Brønsted and Lewis base) in stereo- and



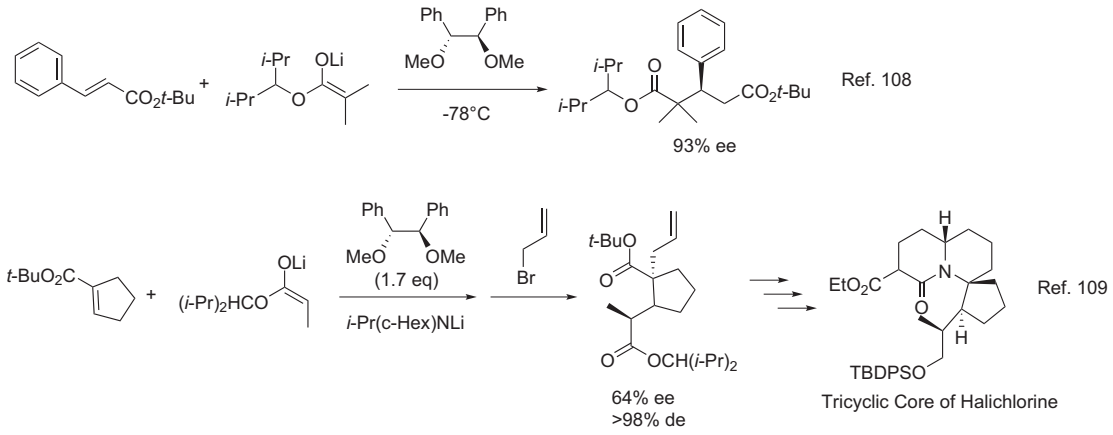
Scheme 47. Asymmetric conjugate addition of organolithiums.



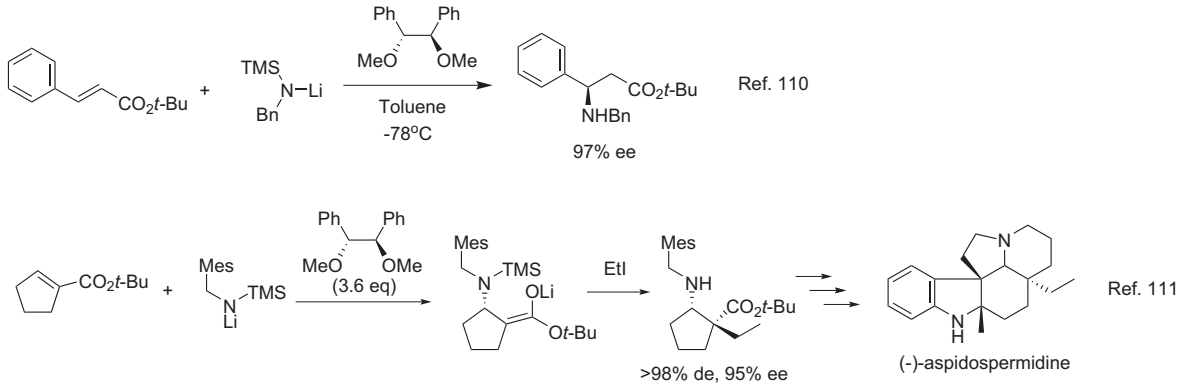
Scheme 48. Asymmetric 1,4-addition to an arene $Cr(CO)_3$ complex.[106]



Scheme 49. Racemic-selective synthesis of azulenyl metallocene catalyst.[107]



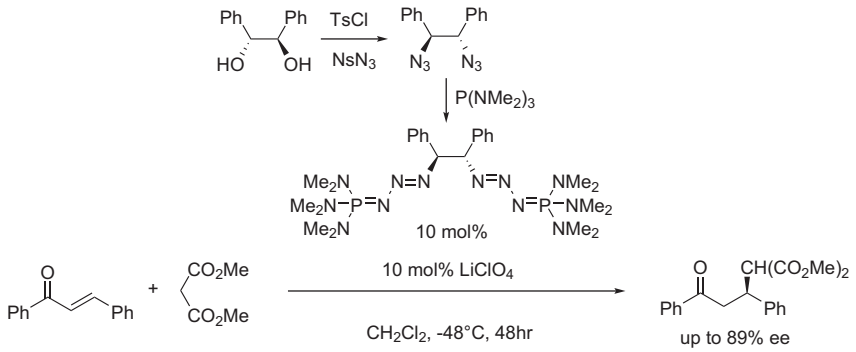
Scheme 50. Asymmetric alkylation of lithium ester enolate.



Scheme 51. Asymmetric 1,4-addition of lithium amide.

chemoselective catalytic transformations.[112] Chiral bisphosphazides complexed with lithium salts efficiently catalyze the direct enantioselective 1,4-addition of dialkyl malonates to acyclic enones. Spectroscopic studies on the stoichiometry of the bisphosphazide and lithium salt have indicated the formation of a 1/1 species as the active enantioselective catalyst (Scheme 52).

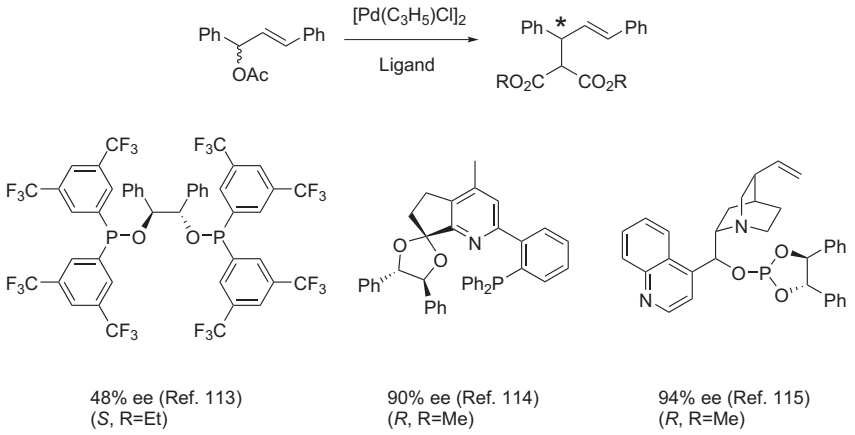
pyrindine-7-one and a series of substituted chiral C_2-symmetric 1,2-ethanediols, and evaluated them for use in catalytic asymmetric synthesis in palladium-catalyzed allylic substitution. He showed that hydrobenzoin is the best ligand in diols (90% ee).[114] Zhang synthesized a novel class of bidentate chiral P,N donor ligands in one pot from hydrobenzoin and cinchona alkaloids in two steps.



Scheme 52. Direct conjugate addition of dialkyl malonates to enones catalyzed by bisphosphazide.[112]

3.2.4. Asymmetric allylic alkylation. Palladium-catalyzed asymmetric allylic alkylation is one of the most explored reactions in chiral chemistry. Among enormous ligands that are used in allylic alkylation, hydrobenzoin is also employed as a chiral ligand. RajanBabu examined several C_2-symmetric diols as precursors of the chiral backbones; however, hydrobenzoin did not show a good result compared with diethyl tartrate or BINOL.[113] Wilson prepared a series of P,N-ligands from 2-chloro-4-methyl-6,7-dihydro-5*H*-[1] Their application to asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate gave the corresponding products in excellent yields and up to 94% ee[115] (Scheme 53).

3.2.5. Asymmetric Diels–Alder reaction. The asymmetric Diels–Alder reaction, catalyzed by a chiral Lewis acid, is a well-examined reaction and applied in many examples of synthesis; however, Lewis acid complexes of hydrobenzoin have not achieve a satisfactory level of

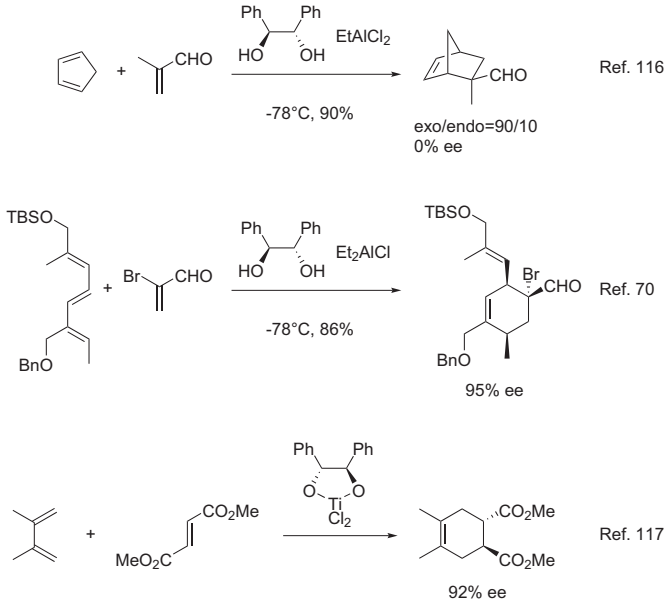


Scheme 53. Palladium-catalyzed asymmetric allylic alkylation using hydrobenzoin as chiral ligand.

results. Kagan reported the application of a chiral diol–aluminum complex prepared from chiral diol and ethyl aluminum dichloride in an asymmetric Diels–Alder reaction of cyclopentadiene; however, hydrobenzoin did not show asymmetric induction (1,1-diphenyl-1,2-propanediol showed the highest ee).[116] Marshall also reported that a chiral hydrobenzoin–aluminum complex prepared from diethyl aluminum chloride gave a Diels–Alder adduct of a particular complex diene in high enantiomeric excess.[70] However, in the case of 1,3-butadiene and α-bromoacrolein, this catalyst resulted in a modest yield and low enantiomeric excess. Oh found that chiral hydrobenzoin–titanium complex promoted an asymmetric Diels–Alder reaction when fumarate ester was used as a dienophile.[117] A Lewis acid complex of bidentate oxygen ligand is widely used in asymmetric Diels–Alder reactions; however, the utility of hydrobenzoin in this application is limited, especially not work for cyclopentadiene (Scheme 54).

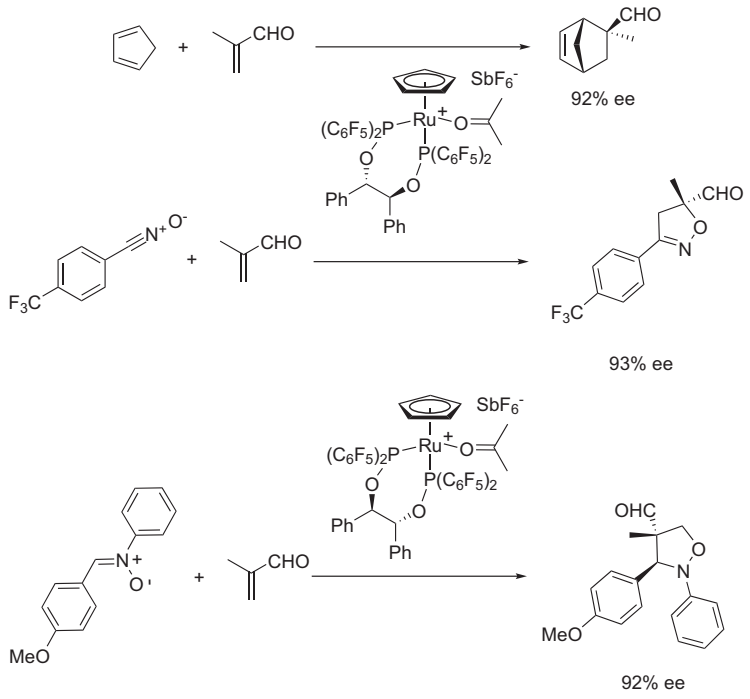
asymmetric induction in the Diels–Alder reaction of dienes with enals.[118] The Diels–Alder reaction of methacrolein with cyclopentadiene, catalyzed by the Ru–BIPHOP-F complex, gave the cycloadduct in 91% yield with a diastereomeric *exo*/*endo* ratio of 97/3 and an enantioselectivity of 92% ee (*exo*). The ligand that was modified at the *meta* position of the ligand backbone phenyl rings, (*S*,*S*)-Me$_4$BIPHOP-F, improved the enantioselectivity of the Diels–Alder reaction of methacrolein and cyclopentadiene to 97% ee.[119] α,β-Unsaturated ketones also gave cycloadducts with cyclopentadiene in the presence of this catalyst.[120] Kündig also shows that this catalyst can be used in 1,3-dipolar cycloaddition of enals with diaryl nitrones[121] and aryl nitrile oxide[122] (Scheme 55).

3.2.6. Asymmetric oxidation of sulfide. After the pioneering work by Kagan and Modena, chiral diols, such as diethyl tartarate are mainly



Scheme 54. Asymmetric Diels–Alder reaction catalyzed by hydrobenzoin–Lewis acid complex.

Kündig's new bidentate ligand, BIPHOP-F, opens new possibilities for Lewis acid catalysts derived from chiral hydrobenzoin. Kündig reported that the Fe and Ru Lewis acids [CpFe(BIPHOP-F)]$^+$ and [CpRu(BIPHOP-F)]$^+$ (BIPHOP-F=1,2-bis-[bis(penta-fluoro-phenyl)phosphanyloxy]-1,2-diphenylethane) gave used as the titanium complex in the asymmetric oxidation of sulfide with hydroperoxide.[123] Hydrobenzoin also can be used in the practical production of chiral sulfoxide by asymmetric oxidation. As the early example, Yamamoto reported that *o*-tolyl-hydrobenzoin showed good enantioselectivity in asymmetric oxidation of sulfide



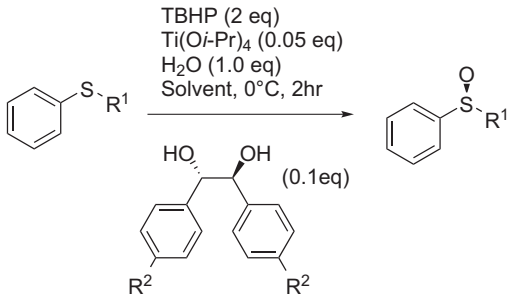
Scheme 55. Asymmetric Diels–Alder reaction 1,3-dipolar cycloaddition catalyzed by BIPHOP-F ligand.[118–122]

using Kagan's 'stoichiometric' procedure, [$Ti(O^iPr)_4$/diol/H_2O/*t*-BuOOH, 1/2/1/1.1].[124]

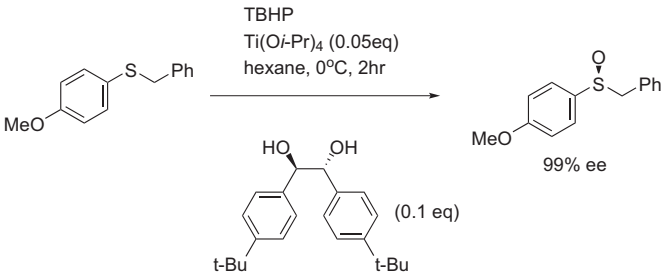
Major progress has been achieved by Rosini, who developed the catalytic asymmetric oxidation of aryl methyl sulfides, mediated by a chiral hydrobenzoin–titanium complex.[125] The asymmetric oxidation of aryl methyl sulfides to sulfoxides with *tert*-butyl hydroperoxide was found to proceed using catalytic amounts of the complex formed in situ between titanium isopropoxide, chiral hydrobenzoin, and water. The chiral sulfoxides are obtained in 60–73% yield and with high enantiomeric excess. It is notable that aryl benzyl sulfides, which are poor substrates for Ti/DET-catalyzed oxidation, afforded 92–99% ee with this oxidation system. However, optimized conditions needed the use of carbon tetrachloride as the solvent, which inhibited its use because of environmental pollution. Recently for this problem, Rosini investigated the effects of the substitution on the aryl moiety of the hydrobenzoins on the asymmetric oxidation of sulfides in detail. The substitution of the aryl ring of the diol with both electron-withdrawing group and electron-donating group substituents generally decreased the enantioselectivity with respect to the use of unsubstituted 1,2-diphenylethane-1,2-diol; however, the 4-*tert*-butyl group substituent raised the enantiomeric excess of the product. Contrary to the other Ti-alcoholates used in the oxidation of sulfides, the Ti-complex of 1,2-di(4-*tert*-butyl)phenyl-1,2-diol was soluble in hexane, enabling it to perform the process with high reactivity and enantioselectivity without chlorinated solvent (Table 8, Scheme 56).[126]

Naso expanded the application of the asymmetric oxidation of sulfide by chiral hydrobenzoin. The benzyl group or *p*-bromophenyl group on sulfoxide is a good leaving group in the stereocontrolled substitution promoted by the Grignard reagent. He synthesized chiral benzyl *p*-bromophenyl sulfoxide and transformed it into chiral dialkyl sulfoxide by sequential substitution reaction (Scheme 57).[127] During this work, Naso investigated the conditions and the reaction mechanism in detail and found some interesting points: (1) compared with diethyl tartarate or BINOL, the effect of the kinetic resolution of sulfoxide by the overoxidation to sulfone is negligible, and (2) in hexane, it is not necessary to add water. When hydrobenzoin of low optical purity was used, the obtained chiral sulfoxide showed higher optical purity than that of hydrobenzoin. This 'positive non-linear effect' and the need for 2 mol equiv of hydrobenzoin to titanium suggest that the active catalyst consists of 2 mol of hydrobenzoin and 1 mol of titanium. Recently, they proposed a reaction mechanism based on DFT computations.[128]

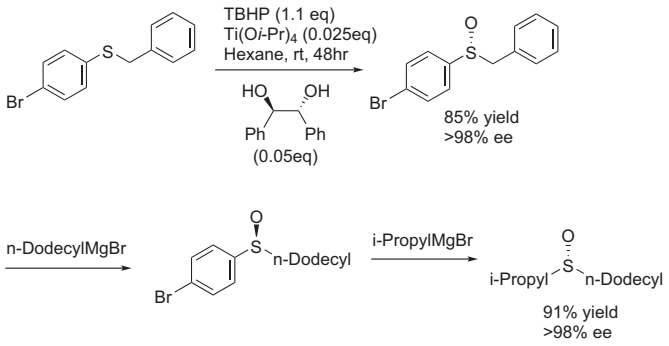
Table 8
Asymmetric oxidation of aryl methyl sulfides[125,126]



R^1	R^2	Solvent	Yield (%)	ee (%)
Me	H	CCl_4	63	80
n-Bu	H	CCl_4	69	80
$PhCH_2$	H	CCl_4	73	>99
Me	*t*-Bu	Hexane	73	82



Scheme 56. Asymmetric oxidation using 1,2-di(4-*tert*-butyl)phenyl-1,2-diol.[126]



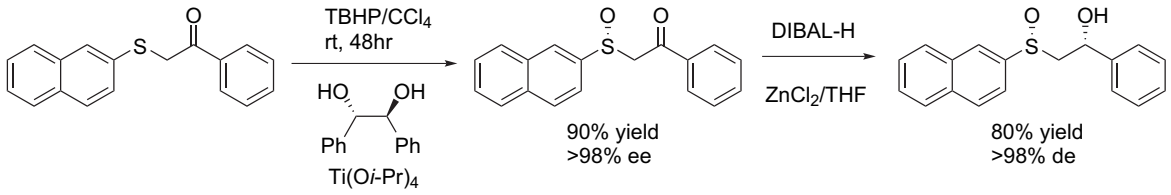
Scheme 57. Preparation of chiral dialkyl sulfoxide by sequential substitution reaction.[127]

This calculation show that stereoselectivity can be explained by the mechanism of the approaching orientations of sulfide to the Ti (hydrobenzoin)$_2$ complex.

Chiral β-keto sulfoxides also can be prepared in 57–90% yields and in 76–98% ee by this reaction system. The use of (*S*,*S*)-hydrobenzoin as the ligand leads to aryl β-keto sulfoxides with (*R*)-configuration at the sulfur and to methyl phenacyl sulfoxide with (*S*)-configuration at the sulfur. Aryl keto sulfoxides are reduced with diisobutylaluminum hydride in the presence of zinc chloride to yield β-sulfinyl alcohols with high diastereoselectivity (Scheme 58).[129]

Sulindac is an anti-inflammatory drug, but recently the application for cancer treatment has became an area of great interest. To date, Sulindac has been used as a racemic mixture. Cardellicchio reported the preparation of an enantiomer of Sulindac by asymmetric oxidation by chiral hydrobenzoin in 94–96% ee with moderate isolated yield (48–50%) (Scheme 59).[131]

3.2.7. Asymmetric epoxidation. Oxone epoxidation using chiral ketones is an important method in the asymmetric oxidation of olefin. Song reported asymmetric epoxidation of unfunctionalized

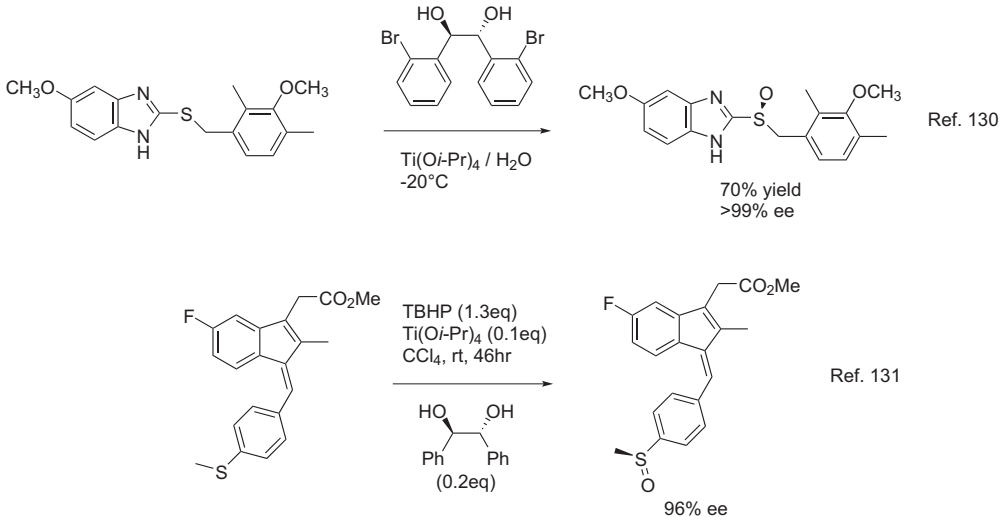


Scheme 58. Preparation of chiral β-sulfinyl alcohol from ketosulfide.[129]

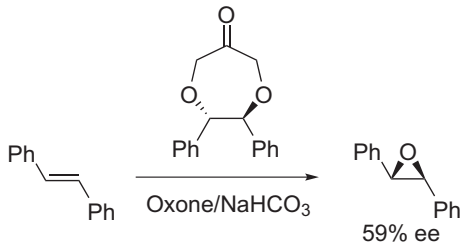
This procedure is used in the preparation of pharmaceuticals containing chiral sulfoxide. Recently, this asymmetric oxidation has been applied to the preparation of various proton-pump inhibitors. Esomeprazole, the enantiomer of Omeprazole, is obtained in high enantiomeric excess by titanium-catalyzed asymmetric oxidation. Jiang reported that *o*-bromohydrobenzoin showed higher enantiomeric excess than simple hydrobenzoin.[130]

olefins using new C_2-symmetric chiral ketone catalysts derived from chiral diol. In the case of stilbene, hydrobenzoin showed a better result compared with BINOL[132] (Scheme 60).

3.2.8. Asymmetric reduction. Metal-catalyzed hydrogenation is the most frequently examined asymmetric reaction in academia and industry. In this area, C_2-axis chiral bisphosphine represented by

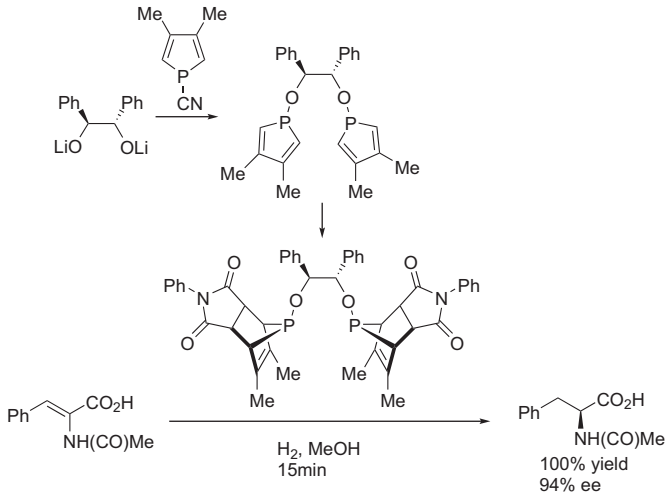


Scheme 59. Preparation of pharmaceuticals containing chiral sulfoxide.



Scheme 60. Asymmetric oxidation of olefin by Oxone–ketone derived from chiral hydrobenzoin.[132]

BINAP is the majority of practical ligand, and the technology has already matured. Unfortunately, bisphosphine ligand derived from chiral hydrobenzoin has not shown successful results; however, recent variations in the phosphorus group in the chiral ligand offer a new area of activity of chiral hydrobenzoin. Mathey reported that bisphosphinite, incorporating two 7-phosphanorbornene subunits, is an efficient ligand for the Rhodium-catalyzed enantioselective hydrogenation of functional alkenes in terms of rate and enantioselectivity.[133] This type of structure is readily accessible by [4+2] cycloaddition of phospholes with dienophilic alkenes and can be easily fine tuned (Scheme 61).



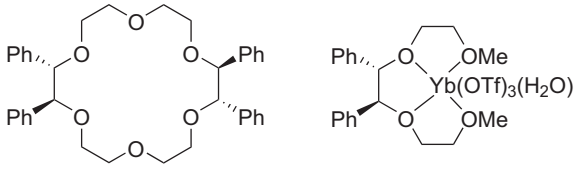
Scheme 61. Asymmetric hydrogenation by bisphosphinite derived from hydrobenzoin.[133]

4. Organic functional material

Not only as the tool of organic synthesis, but also chiral molecules is important as the functional material. Hydrobenzoin also has various examples of applications in organic functional materials. In this case, the specific bulk structures derived from the chirality of hydrobenzoin provides various effects against the properties of the material; therefore, we can see chiral hydrobenzoin in various functional materials. In this chapter, the examples of functional materials containing chiral hydrobenzoin are summarized.

4.1. Polyether podands

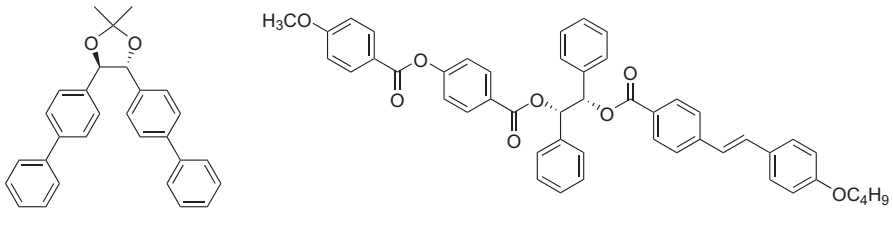
Chiral recognition by crown ether, derived from chiral BINOLs, is Cram's monumental work, which was the basis for his Novel prize. The utilization of chiral hydrobenzoin in host–guest chemistry also has a long history. The first example of crown ether derived from chiral hydrobenzoin (tetraphenyl-l8-crown-6) was reported in 1981 by Hashimoto. He used hydrobenzoin-crown ether for the resolution of racemic amines; however, the enantioselection was a poor result.[134] Stoddart improved the preparation method of tetraphenyl-l8-crown-6.[135] He prepared ammonia–borane complexes of tetraphenyl-l8-crown-6 and applied them to the asymmetric reduction of aromatic ketones; however, the enantiomeric excess was modest[136] Recently, Aspinall reported that a novel series of modular chiral polyether podands derived chiral hydrobenzoin from catalytically active complexes with lanthanide triflates; however, enantioselectivities in the Diels–Alder and carbonyl allylation reactions were very poor (generally 5%)[137] (Scheme 62).



Scheme 62. Polyether podands derived from hydrobenzoin.[134–137]

4.2. Liquid crystal

Liquid crystal is a representative electric device where chiral molecules have an important role to play for the expression of function. Hydrobenzoin is also examined as the chiral structure of liquid crystals (Scheme 63). Rosini reported that a systematic study of the cholesteric induction in nematic solvents by some cyclic derivatives of hydrobenzoin shows that the values of the twisting power are significantly dependent on the nature of the link connecting the two oxygen atoms and on the nature of the *p*,*p*′-substituents. This result has been interpreted, considering that the nature of the bridge affects the overall molecular shape and that the *p*,*p*′-substituents affect both the molecular polarizability and shape. This investigation points out that the polarizability of the solute and the solvent is the main parameter in determining the value of the twisting power, while electrostatic arene–arene interactions contribute to a lesser extent. It has been also observed that solutes having the same structure and the same absolute configuration can induce cholesteric helices of opposite signs, depending on the substituent on the aromatic ring. This finding indicates that configurational assignments by cholesteric induction are reliable only

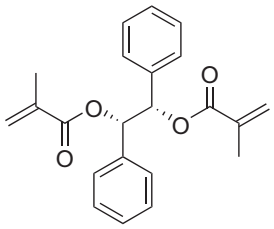


Scheme 63. The example of liquid crystal, which have hydrobenzoin structure.

if high values of twisting power are measured.[138] Greenfield of Merck KGaA reported the application of hydrobenzoin to liquid crystal mixtures. One example exhibits high helical twisting power and improved temperature stability.[139]

4.3. Organic conducting material

The interest in chiral compounds has been increased also by the use of organic compounds as materials for non-linear optical applications in recent years. Many organic molecules and polymers can exhibit high second harmonic generation (SHG) activity. Percino synthesized hydrobenzoin methacrylate (Scheme 64) and evaluated the non-linear optical property of this polymethacrylate.[140] In comparison with other chiral materials, the SHG value of the new hydrobenzoin polymer showed greater efficiency with regard to luminescence emission.



Scheme 64. Hydrobenzoin monomer for the non-linear optical material.[140]

5. Summary

In this review, the author summarized the history and recent topics of the chemistry of chiral hydrobenzoin. The long history of this molecule reflects the advance of chiral chemistry. The various applications that have been developed in this history reveal the wide ability and utility of chiral hydrobenzoin as chiral ligands, chiral auxiliaries, and functional compounds. Recent advances in the practical preparation of chiral hydrobenzoin, including asymmetric dihydroxylation and asymmetric transfer hydrogenation, will contribute both to the preparation of various derivatives of hydrobenzoin for optimization of the structure and to large-scale synthesis in industrial use. As the most useful chiral diol, hydrobenzoin will continue to show various features in the future.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.tet.2011.01.044.

References and notes

1. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
2. Bhowmick, K. C.; Joshi, N. N. *Tetrahedron: Asymmetry* **2006**, *17*, 1901.
3. Collet, A.; Brienne, M. J.; Jacques, J. *Chem. Rev.* **1980**, *80*, 215.
4. Erlenmeyer, E., Jr. *Chem. Ber.* **1897**, *30*, 1531.
5. Fieser, L. F. *Experiments in Organic Chemistry*; D. C. Heath &: Lexington, MA, 1960; p 188.
6. Grimshaw, J.; Ramsey, J. S. *J. Chem. Soc. C* **1966**, 653.
7. Brugidou, J.; Christol, H.; Sales, R. *Bull. Soc. Chim. Fr.* **1974**, 2033.
8. Maillard, D.; Koller, G.; Wakaresko, E.; Gottburg-Reininger, S. PCT Int. Appl. WO 2010/012746, 2010.
9. Knollmüller, M.; Noe, C. R.; Steinbauer, G.; Dungler, K. *Synthesis* **1986**, *6*, 501.
10. Kawashima, M.; Hirayama, A. *Chem. Lett.* **1991**, 763.
11. Periasamy, M.; Ramanathan, C. R.; Prasad, A. S. B.; Kanth, J. V. B. *Enantiomer* **1998**, *3*, 3.
12. Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052.
13. Gissibl, A.; Padie, C.; Hager, M.; Jaroschik, F.; Rasappan, R.; Cuevas-Yanez, E.; Turrin, C.-O.; Caminade, A.-M.; Majoral, J.-P.; Reiser, O. *Org. Lett.* **2007**, *9*, 2895.
14. Mazet, C.; Roseblade, S.; Köhler, V.; Pfaltz, A. *Org. Lett.* **2006**, *8*, 1879.
15. Arai, T.; Mizukami, T.; Yokoyama, N.; Nakazato, D.; Yanagisawa, A. *Synlett* **2005**, 2670.
16. Mizuta, S.; Ohtsubo, Y.; Tsuzuki, T.; Fujimoto, T.; Yamamoto, I. *Tetrahedron Lett.* **2006**, *47*, 8227.
17. Cha, R.-T.; Wang, S.-Y.; Cheng, S.-L. *J. Appl. Polym. Sci.* **2008**, *108*, 845.
18. Caps, V.; Paraskevas, I.; Tsang, S. C. *Chem. Commun.* **2005**, 1781.
19. Lee, B. S.; Mahajan, S.; Janda, K. D. *Tetrahedron Lett.* **2005**, *46*, 4491.
20. Acklin, W.; Kis, Z.; Prelog, V. *Croat. Chem. Acta* **1965**, *37*, 11.
21. Imuta, M.; Ziffer, H. *J. Org. Chem.* **1978**, *43*, 3319.
22. Buisson, D.; Baba, S. E.; Azerad, R. *Tetrahedron Lett.* **1986**, *27*, 4453.
23. Demir, A. S.; Hamamci, H.; Ayhan, P.; Duygu, A. N.; Igdir, A. C.; Capanoglu, D. *Tetrahedron: Asymmetry* **2004**, *15*, 2579.
24. Yamagishi, A. *J. Chem. Soc., Chem. Commun.* **1984**, 119.
25. (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629; (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York, NY, 1994, Chapter 2.
26. Quallich, G. J.; Keavey, K. N.; Woodall, T. M. *Tetrahedron Lett.* **1995**, *36*, 4729.
27. Shimizu, M.; Tsukamoto, K.; Matsutani, T.; Fujisawa, T. *Tetrahedron* **1998**, *54*, 10265.
28. Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1996**, *61*, 3888.
29. Gamble, M. P.; Smith, A. R. C.; Wills, M. *J. Org. Chem.* **1998**, *63*, 6068.
30. Okano, K.; Shirasaki, M.; Iwane, H. Japanese Patent Appl. JP2000–16954, 2000.
31. (a) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119; (b) Ikariya, T.; Hashiguchi, S.; Murata, K.; Noyori, R. *Org. Synth.* **2005**, *82*, 10.
32. http://www.kanto.co.jp/english/siyaku/fuseishokubai.html.
33. Wu, X.; Li, X.; Zanotti-Gerosa, A.; Pettman, A.; Liu, J.; Mills, A. J.; Xiao, J. *Chem.—Eur. J.* **2008**, *14*, 2209.
34. Berti, G.; Bottari, F. *J. Org. Chem.* **1960**, *25*, 1286.
35. Brienne, M. J.; Collet, A. *J. Chem. Res., Synop.* **1978**, 60.
36. Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773.
37. Tschöp, A.; Marx, A.; Sreekanth, A. R.; Schneider, C. *Eur. J. Org. Chem.* **2007**, 2318.
38. Watabe, T.; Akamatsu, K. *Biochim. Biophys. Acta* **1972**, *279*, 297.
39. Dansette, P. M.; Makedonska, V. B.; Jerina, D. M. *Arch. Biochem. Biophys.* **1978**, *187*, 290.
40. Bellucci, G.; Berti, G.; Chiappe, C.; Fabri, F.; Marioni, F. *J. Org. Chem.* **1989**, *54*, 968.
41. Zhao, L.; Han, B.; Huang, Z.; Miller, M.; Huang, H.; Malashock, D. S.; Zhu, Z.; Milan, A.; Robertson, D. E.; Weiner, D. P.; Burk, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 11156.
42. Matsubara, S.; Hashimoto, Y.; Okano, T.; Utimoto, K. *Synlett* **1999**, 1411.
43. Enders, D.; Ullrich, E. C. *Tetrahedron: Asymmetry* **2000**, *11*, 3861.
44. Bensari, A.; Renaud, J.-L.; Riant, O. *Org. Lett.* **2001**, *3*, 3863.
45. Chatterjee, A.; Bennur, T. H.; Joshi, N. N. *J. Org. Chem.* **2003**, *68*, 5668.
46. Yang, H.; Wang, H.; Zhu, C. *J. Org. Chem.* **2007**, *72*, 10029.
47. Sun, J.; Dai, Z.; Li, C.; Pan, X.; Zhu, C. *J. Organomet. Chem.* **2009**, *694*, 3219.
48. Li, Y.-G.; Tian, Q.-S.; Zhao, J.; Feng, Y.; Li, M.-J.; You, T.-P. *Tetrahedron: Asymmetry* **2004**, *15*, 1707.
49. Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198.
50. Ohkuma, T.; Noyori, R. *e-EROS Encycl. Reagents Org. Synth.* **2001**, (CAN 149: 245408).
51. Tanner, D.; Johansson, F.; Harden, A.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 15731.
52. Cho, I.; Meimetis, L.; Britton, R. *Org. Lett.* **2009**, *11*, 1903.
53. (a) Eid, C. N., Jr.; Konopelski, J. P. *Tetrahedron Lett.* **1991**, *32*, 461; (b) Konopelski, J. P.; Deng, H.; Schiemann, K.; Keane, J. M.; Olmstead, M. M. *Synlett* **1998**, 1105.
54. Jung, M. E.; Lew, W. *Tetrahedron Lett.* **1990**, *31*, 623.
55. Maze, F.; Purpura, M.; Bernaud, F.; Mangeney, P.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1957.
56. Boyer, F.-D.; Prange, T.; Ducrot, P.-H. *Tetrahedron: Asymmetry* **2003**, *14*, 1153.
57. Boezio, A. A.; Solberghe, G.; Lauzon, C.; Charette, A. B. *J. Org. Chem.* **2003**, *68*, 3241.
58. Andrus, M. B.; Soma Sekhar, B. B. V.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035.
59. Tan, L.; Yasuda, N.; Yoshikawa, N.; Hartner, F. W.; Eng, K. K.; Leonard, W. R.; Tsay, F.-R.; Volante, R. P.; Tiller, R. D. *J. Org. Chem.* **2005**, *70*, 8027.
60. Mash, E. A.; Torok, D. S. *J. Org. Chem.* **1989**, *54*, 250.
61. Cossy, J.; BouzBouz, S. *Tetrahedron Lett.* **1996**, *37*, 5091.
62. Aavula, B. R.; Cui, Q.; Mash, E. A. *Tetrahedron: Asymmetry* **2000**, *11*, 4681.
63. Corbett, W.L.; Grimsby, J.S.; Haynes, N.-E.; Kester, R.F.; Mahaney, P.E.; Racha, J. K.; Sarabu, R.; Wang, K.; PCT Int. Appl. WO2003095438, 2003.
64. Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1991**, *47*, 5877.
65. Fioravanti, S.; Luna, G.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1997**, *53*, 4779.
66. Konopelski, J. P.; Boehler, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4515.
67. Wallace, T. W.; Wardell, I.; Li, K. D.; Challand, S. R. *J. Chem. Soc., Chem. Commun.* **1991**, 1707.
68. Leeming, P.; Ray, C. A.; Simpson, S. J.; Wallace, T. W.; Ward, R. A. *Tetrahedron* **2003**, *59*, 341.
69. Jung, M. E.; Huang, A. *Org. Lett.* **2000**, *2*, 2659.
70. Marshall, J. A.; Xie, S. *J. Org. Chem.* **1995**, *60*, 7230.
71. Dzierba, C. D.; Zandi, K. S.; Möllers, T.; Shea, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 4711.
72. Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3559.

73. de Meijere, A.; Becker, H.; Stolle, A.; Kozhushkov, S. I.; Bes, M. T.; Salauen, J.; Noltemeyer, M. *Chem.—Eur. J.* **2005**, *11*, 2471.
74. Scafato, P.; Leo, L.; Superchi, S.; Rosini, C. *Tetrahedron* **2002**, *58*, 153.
75. Mikami, K.; Yoshida, A. *Tetrahedron* **2001**, *57*, 889.
76. (a) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555; (b) Matteson, D. S. *Pure Appl. Chem.* **2003**, *75*, 1249.
77. Matteson, D. S.; Man, H. W. *J. Org. Chem.* **1993**, *58*, 6545.
78. O'Donnell, M. J.; Cooper, J. T.; Mader, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2370.
79. de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1995**, *60*, 3895.
80. de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Elena, G.-G.; Rodrıguez, S. *Tetrahedron: Asymmetry* **2000**, *11*, 4473.
81. Busque, F.; Canto, M.; de March, P.; Figueredo, M.; Font, J.; Rodrıguez, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2021.
82. Alibes, R.; Busque, F.; Bardajı, G. G.; de March, P.; Figueredo, M.; Font, J. *Tetrahedron: Asymmetry* **2006**, *17*, 2632.
83. Fujioka, H.; Kitagawa, H.; Nagatomi, Y.; Kita, Y. *J. Org. Chem.* **1996**, *61*, 7309.
84. Fujioka, H.; Sawama, Y.; Kotoku, N. ,; Ohnaka, T.; Okitsu, T.; Murata, N.; Kubo, O.; Li, R.; Kita, Y. *Chem.—Eur. J.* **2007**, *13*, 10225.
85. Fujioka, H.; Ohba, Y.; Nakahara, K.; Takatsuji, M.; Murai, K.; Ito, M.; Kita, Y. *Org. Lett.* **2007**, *9*, 5605.
86. Fujioka, H.; Nakahara, K.; Oki, T.; Hirano, K.; Hayashi, T.; Kita, Y. *Tetrahedron Lett.* **2010**, *51*, 1945.
87. (a) Fujioka, H.; Ohba, Y.; Hirose, H.; Murai, K.; Kita, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 734; (b) Fujioka, H.; Ohba, Y.; Hirose, H.; Nakahara, K.; Murai, K.; Kita, Y. *Tetrahedron* **2008**, *64*, 4233.
88. Lee, Y. J.; Lee, K.; Jung, S. I.; Jeon, H. B.; Kim, K. S. *Tetrahedron* **2005**, *61*, 1987.
89. Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B. T.; Katz, C. E.; Reddy, D. S.; Aube, J. *J. Am. Chem. Soc.* **2003**, *125*, 7914.
90. Taber, D. F.; Neubert, T. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2002**, *124*, 12416.
91. Taber, D. F.; Sikkander, M. I.; Storck, P. H. *J. Org. Chem.* **2007**, *72*, 4098.
92. Fujioka, H.; Kotoku, N.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **2000**, *41*, 1829.
93. Ishimaru, K.; Monda, K.; Yamamoto, Y.; Akiba, K. *Tetrahedron* **1998**, *54*, 727.
94. Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24.
95. Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481.
96. Suzuki, T.; Yamagiwa, N.; Matsuo, Y.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M.; Noyori, R. *Tetrahedron Lett.* **2001**, *42*, 4669.
97. Hamada, T.; Manabe, K.; Ishikawa, S.; Nagayama, S.; Shiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 2989.
98. Stodulski, M.; Jazwinski, J.; Mlynarski, J. *Eur. J. Org. Chem.* **2008**, 5553.
99. Rosini, C.; Franzini, L.; Pini, D.; Salvadori, P. *Tetrahedron: Asymmetry* **1990**, *1*, 587.
100. Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 1957.
101. Dean, M. A.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2008**, *19*, 2563.
102. (a) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266; (b) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351.
103. Xu, F.; Tillyer, R. D.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron: Asymmetry* **1998**, *9*, 1651.
104. Yamada, K.; Yamashita, M.; Sumiyoshi, T.; Nishimura, K.; Tomioka, K. *Org. Lett.* **2009**, *11*, 1631.
105. Amurrio, D.; Khan, K.; Kündig, E. P. *J. Org. Chem.* **1996**, *61*, 2258.
106. Fretzen, A.; Kündig, E. P. *Helv. Chim. Acta* **1997**, *80*, 2023.
107. Hayashi, T.; Ogasawara, M.; Miyauchi, H.; Sumitani, N.; Okano, K. Japanese patent application, JP2001163893, 2001.
108. Yamamoto, Y.; Suzuki, H.; Yasuda, Y.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **2008**, *49*, 4582.
109. Yamamoto, Y.; Yasuda, Y.; Nasu, H.; Tomioka, K. *Org. Lett.* **2009**, *11*, 2007.
110. Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2886.
111. Suzuki, M.; Kawamoto, Y.; Sakai, T.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2009**, *11*, 653.
112. Naka, H.; Kanase, N.; Ueno, M.; Kondo, Y. *Chem.—Eur. J.* **2008**, *14*, 5267.
113. Clyne, D. S.; Mermet-Bouvier, Y. C.; Nomura, N.; RajanBabu, T. V. *J. Org. Chem.* **1999**, *64*, 7601.
114. Lyle, M. P. A.; Narine, A. A.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 5060.
115. Wang, Q.-F.; He, W.; Liu, X.-Y.; Chen, H.; Qin, X.-Y.; Zhang, S.-Y. *Tetrahedron: Asymmetry* **2008**, *19*, 2447.
116. Rebiere, F.; Riant, O.; Kagan, H. B. *Tetrahedron: Asymmetry* **1990**, *1*, 199.
117. Devine, P. N.; Oh, T. *J. Org. Chem.* **1992**, *57*, 396.
118. (a) Bruin, M. E.; Kündig, E. P. *Chem. Commun.* **1998**, 2635; (b) Kündig, E. P.; Saudan, C. M.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1220.
119. Kündig, E. P.; Saudan, C. M.; Viton, F. *Adv. Synth. Catal.* **2001**, *343*, 51.
120. Rickerby, J.; Vallet, M.; Bernardinelli, G.; Viton, F.; Kündig, E. P. *Chem.—Eur. J.* **2007**, *13*, 3354.
121. Viton, F.; Bernardinelli, G.; Kündig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968.
122. Brinkmann, Y.; Madhushaw, R. J.; Jazzar, R.; Bernardinelli, G.; Kündig, E. P. *Tetrahedron* **2007**, *63*, 8413.
123. (a) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325; (b) Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984**, 25.
124. Yamamoto, K.; Ando, H.; Shuetake, T.; Ando, H. *J. Chem. Soc., Chem. Commun.* **1989**, 754.
125. (a) Superchi, S.; Rosini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 349; (b) Donnoli, M. I.; Superchi, S.; Rosini, C. *J. Org. Chem.* **1998**, *63*, 9392.
126. Superchi, S.; Scafato, P.; Restaino, L.; Rosini, C. *Chirality* **2008**, *20*, 592.
127. Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Rosito, V. *J. Org. Chem.* **2002**, *67*, 7289.
128. Naso, F.; Capozzi, M. A. M.; Bottoni, A.; Calvaresi, M.; Bertolasi, V.; Capitelli, F.; Cardellicchio, C. *Chem.—Eur. J.* **2009**, *15*, 13417.
129. Cardellicchio, C.; Hassan Omar, O.; Naso, F.; Capozzi, M. A. M.; Capitelli, F.; Bertolasi, V. *Tetrahedron: Asymmetry* **2006**, *17*, 223.
130. Jiang, B.; Zhao, X.-L.; Dong, J.-J.; Wang, W.-J. *Eur. J. Org. Chem.* **2009**, 987.
131. Naso, F.; Cardellicchio, C.; Affortunato, F.; Capozzi, M. A. M. *Tetrahedron: Asymmetry* **2006**, *17*, 3226.
132. Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S.-G.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921.
133. Clochard, M.; Mattmann, E.; Mercier, F.; Ricard, L.; Mathey, F. *Org. Lett.* **2003**, *5*, 3093.
134. Yamashita, J.; Minagawa, M.; Sonobe, A.; Ohashi, S.; Kawamura, M.; Shimizu, K.; Hashimoto, H. *Chem. Lett.* **1982**, *9*, 1409.
135. Crosby, J.; Fakley, M. E.; Gemmell, C.; Martin, K.; Quick, A.; Slawin, A. M. Z.; Shahriari-Zavareh, H.; Stoddart, J. F.; Williams, D. J. *Tetrahedron Lett.* **1989**, *30*, 3849.
136. Stoddart, J. F. *Biochem. Soc. Trans.* **1987**, *15*, 1188.
137. Aspinall, H. C.; Greeves, N.; McIver, E. G. *Tetrahedron* **2003**, *59*, 10453.
138. Superchi, S.; Donnoli, M. I.; Proni, G.; Spada, G. P.; Rosini, C. *J. Org. Chem.* **1999**, *64*, 4762.
139. Vaughan-Spickers, J.; Dunn, C.; Harding, R.; Hassall, I.; Jenkins, T.; May, A.; Greenfield, S. PCT Int. Appl. WO2002040614, 2002.
140. Percino, M. J.; Chapela, V. M.; Ortega-Martinez, R. *Des. Monomers Polym.* **2004**, *7*, 435.
141. Onomura, O.; Arimoto, H.; Matsumura, Y.; Demizu, Y. *Tetrahedron Lett.* **2007**, *48*, 8668.
142. Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302.
143. (a) Ding, K.; Uozumi, Y. *Handbook of Asymmetric Heterogeneous Catalysis*; Wiley-VCH: Verlag, 2008; (b) Kobayashi, S.; Sugiura, M. *Adv. Synth. Catal.* **2006**, *348*, 1496.

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